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TITLE OF THE INVENTION (280 characters max)

PHARMACEUTICAL COMPOUNDS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

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☒ Application Data Sheet. See 37 CFR 1.76

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☐ Other (specify)

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Respectfully submitted,

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REGISTRATION NO. *(if appropriate)* 32,700

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Applicant: Berdini et al.

Title: PHARMACEUTICAL COMPOUNDS

Attorney Docket No.: 2245.006A(P)

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APPLICATION DATA SHEET

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Title of Invention	PHARMACEUTICAL COMPOUNDS

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ttorney Docket Number: 2245.006A(P)

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PHARMACEUTICAL COMPOUNDS

This invention relates to pyrazole-containing aryl- and heteroaryl-alkylamine compounds that inhibit or modulate the activity of protein kinase A (PKA) and protein kinase B (PKB), to the use of the compounds in the treatment or prophylaxis of disease states or conditions mediated by PKA and PKB, and to novel compounds having PKA and PKB inhibitory or modulating activity. Also provided are pharmaceutical compositions containing the compounds and novel chemical intermediates.

Background of the Invention

Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a wide variety of signal transduction processes within the cell (Hardie, G. and Hanks, S. (1995) *The Protein Kinase Facts Book. I and II,* Academic Press, San Diego, CA). The kinases may be categorized into families by the substrates they phosphorylate (e.g., protein-tyrosine, protein-serine/threonine, lipids, etc.). Sequence motifs have been identified that generally correspond to each of these kinase families (e.g., Hanks, S.K., Hunter, T., *FASEB J.,* 9:576-596 (1995); Knighton, *et al., Science,* 253:407-414 (1991); Hiles, *et al., Cell,* 70:419-429 (1992); Kunz, *et al., Cell,* 73:585-596 (1993); Garcia-Bustos, *et al., EMBO J.,* 13:2352-2361 (1994)).

Protein kinases may be characterized by their regulation mechanisms. These mechanisms include, for example, autophosphorylation, transphosphorylation by other kinases, protein-protein interactions, protein-lipid interactions, and protein-polynucleotide interactions. An individual protein kinase may be regulated by more than one mechanism.

Kinases regulate many different cell processes including, but not limited to, proliferation, differentiation, apoptosis, motility, transcription, translation and other signalling processes, by adding phosphate groups to target proteins. These phosphorylation events act as molecular on/off switches that can modulate or regulate the target protein biological function. Phosphorylation of target proteins

occurs in response to a variety of extracellular signals (hormones, neurotransmitters, growth and differentiation factors, etc.), cell cycle events, environmental or nutritional stresses, etc. The appropriate protein kinase functions in signalling pathways to activate or inactivate (either directly or indirectly), for example, a metabolic enzyme, regulatory protein, receptor, cytoskeletal protein, ion channel or pump, or transcription factor. Uncontrolled signalling due to defective control of protein phosphorylation has been implicated in a number of diseases, including, for example, inflammation, cancer, allergy/asthma, diseases and conditions of the immune system, diseases and conditions of the central nervous system, and angiogenesis.

Apoptosis or programmed cell death is an important physiological process which removes cells no longer required by an organism. The process is important in early embryonic growth and development allowing the non-necrotic controlled breakdown, removal and recovery of cellular components. The removal of cells by apoptosis is also important in the maintenance of chromosomal and genomic integrity of growing cell populations. There are several known checkpoints in the cell growth cycle at which DNA damage and genomic integrity are carefully monitored. The response to the detection of anomalies at such checkpoints is to arrest the growth of such cells and initiate repair processes. If the damage or anomalies cannot be repaired then apoptosis is initiated by the damaged cell in order to prevent the propagation of faults and errors. Cancerous cells consistently contain numerous mutations, errors or rearrangements in their chromosomal DNA. It is widely believed that this occurs in part because the majority of tumours have a defect in one or more of the processes responsible for initiation of the apoptotic process. Normal control mechanisms cannot kill the cancerous cells and the chromosomal or DNA coding errors continue to be propagated. As a consequence restoring these pro-apoptotic signals or suppressing unregulated survival signals is an attractive means of treating cancer.

The signal transduction pathway containing the enzymes phosphatidylinositol 3-kinase (PI3K), PDK1 and PKB amongst others, has long been known to mediate increased resistance to apoptosis or survival responses in many cells. There is a

substantial amount of data to indicate that this pathway is an important survival pathway used by many growth factors to suppress apoptosis. The enzyme PI3K is activated by a range of growth and survival factors e.g. EGF, PDGF and through the generation of polyphosphatidylinositols, initiates the activation of the downstream signalling events including the activity of the kinases PDK1 and protein kinase B (PKB) also known as akt. PKB is a protein ser/thr kinase consisting of a kinase domain together with an N-terminal PH domain and C-terminal regulatory domain. The enzyme PKB itself is phosphorylated on Thr 308 by PDK1 and on Ser 473 by an as yet unidentified kinase. Full activation requires phosphorylation at both sites whilst association between PIP3 and the PH domain is required for anchoring of the enzyme to the cytoplasmic face of the lipid membrane providing optimal access to substrates.

Activated PKB in turns phosphorylates a range of substrates contributing to the overall survival response. Whilst we cannot be certain that we understand all of the factors responsible for mediating the PKB dependent survival response, some important actions are believed to be phosphorylation and inactivation of the pro-apoptotic factor BAD and caspase 9, phosphorylation of Forkhead transcription factors e.g. FKHR leading to their exclusion from the nucleus, and activation of the NfkappaB pathway by phosphorylation of upstream kinases in the cascade.

In addition to the anti-apoptotic and pro-survival actions of the PKB pathway, the enzyme also plays an important role in promoting cell proliferation. This action is again likely to be mediated via several actions, some of which are thought to be phosphorylation and inactivation of the cyclin dependent kinase inhibitor of $p21^{Cip1/WAF1}$, and phosphorylation and activation of mTOR, a kinase controlling several aspects of cell growth.

The phosphatase PTEN which dephosphorylates and inactivates polyphosphatidyl-inositols is a key tumour suppressor protein which normally acts to regulate the PI3K/PKB survival pathway. The significance of the PI3K/PKB pathway in tumourigenesis can be judged from the observation that PTEN is one of the most common targets of mutation in human tumours, with mutations in this phosphatase

having been found in ~50% or more of melanomas (Guldberg et al 1997, Cancer Research 57, 3660-3663) and advanced prostate cancers (Cairns et al 1997 Cancer Research 57, 4997). These observations and others suggest that a wide range of tumour types are dependent on the enhanced PKB activity for growth and survival and would respond therapeutically to appropriate inhibitors of PKB.

There are 3 closely related isoforms of PKB called alpha, beta and gamma, which genetic studies suggest have distinct but overlapping functions. Evidence suggests that they can all independently play a role in cancer. For example PKB beta has been found to be over-expressed or activated in 10 – 40% of ovarian and pancreatic cancers (Bellacosa et al 1995, Int. J. Cancer 64, 280 – 285; Cheng et al 1996, PNAS 93, 3636-3641; Yuan et al 2000, Oncogene 19, 2324 – 2330), PKB alpha is amplified in human gastric, prostate and breast cancer (Staal 1987, PNAS 84, 5034 – 5037; Sun et al 2001, Am. J. Pathol. 159, 431 –437) and increased PKB gamma activity has been observed in steroid independent breast and prostate cell lines (Nakatani et al 1999, J. Biol. Chem. 274, 21528 – 21532).

The PKB pathway also functions in the growth and survival of normal tissues and may be regulated during normal physiology to control cell and tissue function. Thus disorders associated with undesirable proliferation and survival of normal cells and tissues may also benefit therapeutically from treatment with a PKB inhibitor. Examples of such disorders are disorders of immune cells associated with prolonged expansion and survival of cell population leading to a prolonged or up regulated immune response. For example, T and B lymphocyte response to cognate antigens or growth factors such as interferon gamma activates the PI3K/PKB pathway and is responsible for maintaining the survival of the antigen specific lymphocyte clones during the immune response. Under conditions in which lymphocytes and other immune cells are responding to inappropriate self or foreign antigens, or in which other abnormalities lead to prolonged activation, the PKB pathway contributes an important survival signal preventing the normal mechanisms by which the immune response is terminated via apoptosis of the activated cell population. There is a considerable amount of evidence demonstrating the expansion of lymphocyte populations responding to self

antigens in autoimmune conditions such as multiple sclerosis and arthritis. Expansion of lymphocyte populations responding inappropriately to foreign antigens is a feature of another set of conditions such as allergic responses and asthma. In summary inhibition of PKB could provide a beneficial treatment for immune disorders.

Other examples of inappropriate expansion, growth, proliferation, hyperplasia and survival of normal cells in which PKB may play a role include but are not limited to atherosclerosis, cardiac myopathy and glomerulonephritis.

In addition to the role in cell growth and survival, the PKB pathway functions in the control of glucose metabolism by insulin. Available evidence from mice deficient in the alpha and beta isoforms of PKB suggests that this action is mediated by the beta isoform. As a consequence, modulators of PKB activity may also find utility in diseases in which there is a dysfunction of glucose metabolism such as diabetes.

Cyclic AMP-dependent protein kinase (PKA) is a serine/threonine protein kinase that phosphorylates a wide range of substrates and is involved in the regulation of many cellular processes including cell growth, cell differentiation, ion-channel conductivity, gene transcription and synaptic release of neurotransmitters. In its inactive form, the PKA holoenzyme is a tetramer comprising two regulatory subunits and two catalytic subunits.

PKA acts as a link between G-protein mediated signal transduction events and the cellular processes that they regulate. Binding of a hormone ligand such as glucagon to a transmembrane receptor activates a receptor-coupled G-protein (GTP-binding and hydrolyzing protein). Upon activation, the alpha subunit of the G protein dissociates and binds to and activates adenylate cyclase, which in turn converts ATP to cyclic-AMP (cAMP). The cAMP thus produced then binds to the regulatory subunits of PKA leading to dissociation of the associated catalytic subunits. The catalytic subunits of PKA, which are inactive when associated with the regulatory sub-units, become active upon dissociation and take part in the phosphorylation of other regulatory proteins.

For example, the catalytic sub-unit of PKA phosphorylates the kinase Phosphorylase Kinase which is involved in the phosphorylation of Phosphorylase, the enzyme responsible for breaking down glycogen to release glucose. PKA is also involved in the regulation of glucose levels by phosphorylating and deactivating glycogen synthase. Thus, PKA may be useful in the treatment or management of diseases in which there is a dysfunction of glucose metabolism such as diabetes.

PKA has also been established as an acute inhibitor of T cell activation. Anndahl *et al,* have investigated the possible role of PKA type I in HIV-induced T cell dysfunction on the basis that T cells from HIV-infected patients have increased levels of cAMP and are more sensitive to inhibition by cAMP analogues than are normal T cells. From their studies, they concluded that increased activation of PKA type I may contribute to progressive T cell dysfunction in HIV infection and that PKA type I may therefore be a potential target for immunomodulating therapy.-Aandahl, E. M., Aukrust, P., Skålhegg, B. S., Müller, F., Frøland, S. S., Hansson, V., Taskén, K. *Protein kinase A type I antagonist restores immune responses of T cells from HIV-infected patients*. *FASEB J.* 12, 855--862 (1998).

Because of the diversity and importance of PKA as a messenger in cell regulation, abnormal responses of cAMP leads to a variety of human diseases derived from this, such as irregular cell growth and proliferation (Stratakis, C.A.; Cho-Chung, Y.S.; Protein Kinase A and human diseases. *Trends Endrocri. Metab.* 2002, 13, 50-52). Over-expression of PKA has been observed in a variety of human cancer cells including those from ovarian, breast and colon patients. Inhibition of PKA would therefore be an approach to treatment of cancer (Li, Q.; Zhu, G-D.; *Current Topics in Medicinal Chemistry*, 2002, 2, 939-971).

For a review of the role of PKA in human disease, see for example, *Protein Kinase A and Human Disease*, Edited by Constantine A. Stratakis, Annals of the New York Academy of Sciences, Volume 968, 2002, ISBN 1-57331-412-9.

Several classes of compounds have been disclosed as having PKA and PKB inhibitory activity.

P033 (US2)

For example, a class of isoquinolinyl-sulphonamido-diamines having PKB inhibitory activity is disclosed in WO 01/91754 (Yissum).

WOO/07996 (Chiron) discloses substituted pyrazoles having estrogen receptor agonist activity. The compounds are described as being useful in treatingor preventing *inter alia* estrogen-receptor mediated breast cancer. PKB inhibitory activity is not disclosed.

WO 00/31063 (Searle) discloses substituted pyrazole compounds as p38 kinase inhibitors.

WO 01/32653 (Cephalon) discloses a class of pyrazolone kinase inhibitors.WO 03/059884 (X-Ceptor Therapeutics) discloses N-substituted pyridine compounds as modulators of nuclear receptors.

WO 03/068230 (Pharmacia) discloses substituted pyridones as p38 MAP kinase modulators.

Summary of the Invention

The invention provides compounds that have protein kinase A (PKA) and protein B (PKB) inhibiting or modulating activity, and which it is envisaged will be useful in preventing or treating disease states or conditions mediated by PKA or PKB.

Accordingly, in one aspect, the invention provides novel compounds of the formula (I) as defined herein.

The invention also provides a compound of the formula (I) as defined herein for use in the prophylaxis or treatment of a disease state or condition mediated by protein kinase A or protein kinase B.

The invention also provides the use of a compound of the formula (I) as defined herein for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by protein kinase A or protein kinase B.

In a further aspect, the invention provides a method for the prophylaxis or treatment of a disease state or condition mediated by protein kinase A or protein kinase B, which method comprises administering to a subject in need thereof a compound of the formula (I) as defined herein.

The invention further provides a method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, the method comprising administering to the mammal a compound of the formula (I) as defined herein in an amount effective to inhibit protein kinase A or protein kinase B activity.

In another aspect, the invention provides a method of inhibiting protein kinase A or protein kinase B, which method comprises contacting the kinase with a kinase-inhibiting compound of the formula (I) as defined herein.

The invention further provides a method of modulating a cellular process (for example cell division) by inhibiting the activity of a protein kinase A or a protein kinase B using a compound of the formula (I) as defined herein.

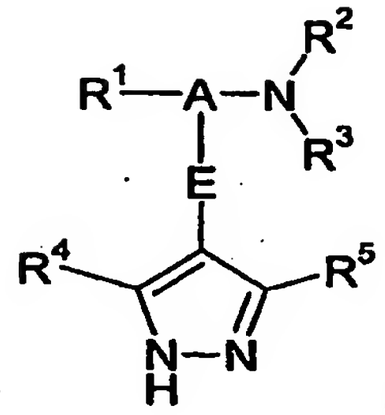
The invention also provides the use of a compound of the formula (I) as defined herein for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition arising from abnormal cell growth.

The invention also provides a method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, which method comprises administering to the mammal a compound of the formula (I) as defined herein in an amount effective in inhibiting abnormal cell growth.

In a further aspect, the invention provides a pharmaceutical composition comprising a novel compound of the formula (I) as hereinbefore defined and a pharmaceutically acceptable carrier.

The invention also provides compounds of the formula (I) for use in medicine.

The compounds of the invention are represented by the general formula (I):



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wherein A is a saturated hydrocarbon linker group containing from 1 to 7 carbon atoms, the linker group having a maximum chain length of 5 atoms extending between R^1 and NR^2R^3 and a maximum chain length of 4 atoms extending between E and NR^2R^3, wherein one of the carbon atoms in the linker group may optionally be replaced by an oxygen or nitrogen atom; and wherein the carbon atoms of the linker group A may optionally bear one or more substituents selected from oxo, fluorine and hydroxy, provided that the hydroxy group when present is not located at a carbon atom α with respect to the NR^2R^3 group and provided that the oxo group when present is located at a carbon atom α with respect to the NR^2R^3 group;

E is a monocyclic or bicyclic carbocyclic or heterocyclic group;

R^1 is an aryl or heteroaryl group;

R^2 and R^3 are independently selected from hydrogen, C_{1-4} hydrocarbyl and C_{1-4} acyl;

or R^2 and R^3 together with the nitrogen atom to which they are attached form a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N;

or one of R^2 and R^3 together with the nitrogen atom to which they are attached and one or more atoms from the linker group A form a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N;

or NR^2R^3 and the carbon atom of linker group A to which it is attached together form a cyano group;

R^4 is selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, cyano, and CF_3; and

R^5 is selected from selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, cyano, $CONH_2$, $CONHR^9$, CF_3, NH_2, $NHCOR^9$ or $NHCONHR^9$;

R^9 is phenyl or benzyl each optionally substituted by one or substituents selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

X^1 is O, S or NR^c and X^2 is =O, =S or =NR^c.

General Preferences and Definitions

The following general preferences and definitions shall apply to each of the moieties A, E and R^1 to R^5 and R^9 and any sub-definition, sub-group or embodiment thereof, unless the context indicates otherwise.

Any references to Formula (I) herein shall be taken also to refer to formula (II) and any other sub-group of compounds within formula (I) unless the context requires otherwise.

References to "carbocyclic" and "heterocyclic" groups as used herein shall, unless the context indicates otherwise, include both aromatic and non-aromatic ring systems. In general, such groups may be monocyclic or bicyclic and may contain, for example, 3 to 12 ring members, more usually 5 to 10 ring members. Examples of monocyclic groups are groups containing 3, 4, 5, 6, 7, and 8 ring members, more usually 3 to 7, and preferably 5 or 6 ring members. Examples of bicyclic groups are those containing 8, 9, 10, 11 and 12 ring members, and more usually 9 or 10 ring members.

The carbocyclic or heterocyclic groups can be aryl or heteroaryl groups having from 5 to 12 ring members, more usually from 5 to 10 ring members. The term "aryl" as used herein refers to a carbocyclic group having aromatic character and the term "heteroaryl" is used herein to denote a heterocyclic group having aromatic character. The terms "aryl" and "heteroaryl" embrace polycyclic (e.g. bicyclic) ring systems wherein one or more rings are non-aromatic, provided that at least one ring is aromatic. In such polycyclic systems, the group may be attached by the aromatic ring, or by a non-aromatic ring. The aryl or heteroaryl groups can be monocyclic or bicyclic groups and can be unsubstituted or substituted with one or more substituents, for example one or more groups R^{10} as defined herein.

The term non-aromatic group embraces unsaturated ring systems without aromatic character, partially saturated and fully saturated carbocyclic and heterocyclic ring systems. The terms "unsaturated" and "partially saturated" refer to rings wherein the ring structure(s) contains atoms sharing more than one valence bond i.e. the ring contains at least one multiple bond e.g. a C=C, C≡C or N=C bond. The term "fully saturated" refers to rings where there are no multiple bonds between ring atoms. Saturated carbocyclic groups include cycloalkyl groups as defined below. Partially saturated carbocyclic groups include cycloalkenyl groups as defined below, for example cyclopentenyl, cycloheptenyl and cyclooctenyl.

Examples of heteroaryl groups are monocyclic and bicyclic groups containing from five to twelve ring members, and more usually from five to ten ring members. The heteroaryl group can be, for example, a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings. Each ring may contain up to about four heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heteroaryl ring will contain up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl

rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five.

Examples of five membered heteroaryl groups include but are not limited to pyrrole, furan, thiophene, imidazole, furazan, oxazole, oxadiazole, oxatriazole, isoxazole, thiazole, isothiazole, pyrazole, triazole and tetrazole groups.

Examples of six membered heteroaryl groups include but are not limited to pyridine, pyrazine, pyridazine, pyrimidine and triazine.

Examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring include but are not limited to benzfuran, benzthiophene, benzimidazole, benzoxazole, benzisoxazole, benzthiazole, benzisothiazole, isobenzofuran, indole, isoindole, indolizine, indoline, isoindoline, purine (e.g., adenine, guanine), indazole, benzodioxole and pyrazolopyridine groups.

Examples of bicyclic heteroaryl groups containing two fused six membered rings include but are not limited to quinoline, isoquinoline, chroman, thiochroman, chromene, isochromene, chroman, isochroman, benzodioxan, quinolizine, benzoxazine, benzodiazine, pyridopyridine, quinoxaline, quinazoline, cinnoline, phthalazine, naphthyridine and pteridine groups.

Examples of polycyclic aryl and heteroaryl groups containing an aromatic ring and a non-aromatic ring include tetrahydronaphthalene, tetrahydroisoquinoline, tetrahydroquinoline, dihydrobenzthiene, dihydrobenzfuran, 2,3-dihydro-benzo[1,4]dioxine, benzo[1,3]dioxole, 4,5,6,7-tetrahydrobenzofuran, indoline and indane groups.

Examples of carbocyclic aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl groups.

Examples of non-aromatic heterocyclic groups are groups having from 3 to 12 ring members, more usually 5 to 10 ring members. Such groups can be monocyclic or bicyclic, for example, and typically have from 1 to 5 heteroatom ring members (more usually 1, 2, 3 or 4 heteroatom ring members), usually selected from nitrogen, oxygen and sulphur. The heterocylic groups can contain, for example, cyclic ether moieties (e.g as in tetrahydrofuran and dioxane), cyclic thioether moieties (e.g. as in tetrahydrothiophene and dithiane), cyclic amine moieties (e.g. as in pyrrolidine), cyclic amide moieties (e.g. as in pyrrolidone), cyclic ester moieties (e.g. as in butyrolactone), cyclic sulphones (e.g. as in sulfolane and sulfolene), cyclic sulphoxides, cyclic sulphonamides and combinations thereof (e.g. thiomorpholine).

Particular examples include morpholine, piperidine (e.g. 1-piperidinyl, 2-piperidinyl 3-piperidinyl and 4-piperidinyl), piperidone, pyrrolidine (e.g. 1-pyrrolidinyl, 2-pyrrolidinyl and 3-pyrrolidinyl), pyrrolidone, azetidine, pyran (2H-pyran or 4H-pyran), dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole, tetrahydrofuran, tetrahydrothiophene, dioxane, tetrahydropyran (e.g. 4-tetrahydro pyranyl), imidazoline, imidazolidinone, oxazoline, thiazoline, 2-pyrazoline, pyrazolidine, piperazone, piperazine, and N-alkyl piperazines such as N-methyl piperazine. In general, preferred non-aromatic heterocyclic groups include piperidine, pyrrolidine, azetidine, morpholine, piperazine and N-alkyl piperazines.

Examples of non-aromatic carbocyclic groups include cycloalkane groups such as cyclohexyl and cyclopentyl, cycloalkenyl groups such as cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl, as well as cyclohexadienyl, cyclooctatetraene, tetrahydronaphthenyl and decalinyl.

Each of the definitions of carbocyclic and heterocyclic groups in this specification may optionally exclude any one or any combination of two or more of the following moieties:

- substituted or unsubstituted pyridone rings;
- substituted or unsubstituted pyrrolo[1,2-a]pyrimid-4-ones;
- substituted or unsubstituted pyrazolones.

Where reference is made herein to carbocyclic and heterocyclic groups, the carbocyclic or heterocyclic ring can, unless the context indicates otherwise, be unsubstituted or substituted by one or more substituent groups R^{10} selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

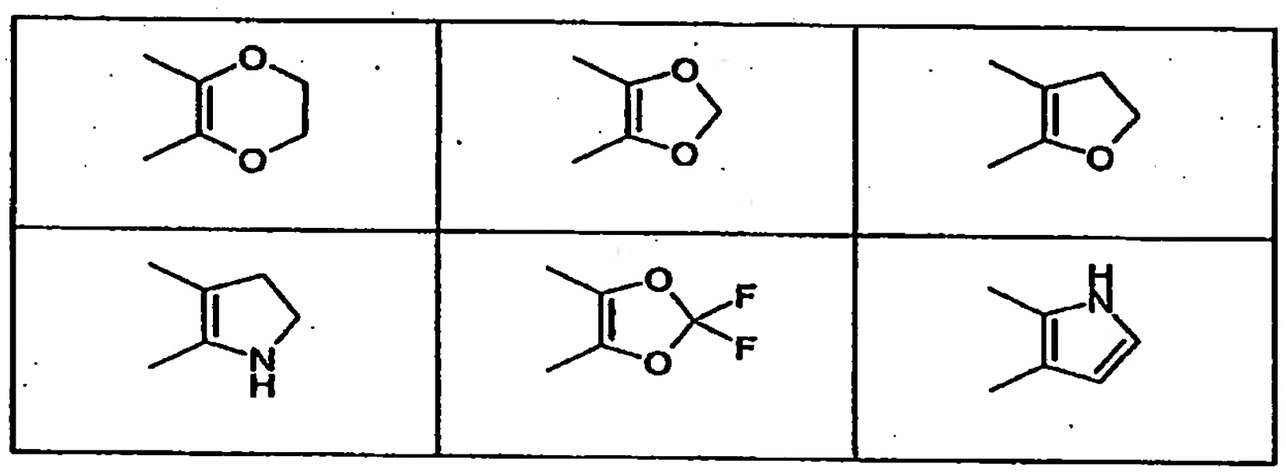
R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

X^1 is O, S or NR^c and X^2 is =O, =S or =NR^c.

Where the substituent group R^{10} comprises or includes a carbocyclic or heterocyclic group, the said carbocyclic or heterocyclic group may be unsubstituted or may itself be substituted with one or more further substituent groups R^{10}. In one sub-group of compounds of the formula (I), such further substituent groups R^{10} may include carbocyclic or heterocyclic groups, which are typically not themselves further substituted. In another sub-group of compounds of the formula (I), the said further substituents do not include carbocyclic or heterocyclic groups but are otherwise selected from the groups listed above in the definition of R^{10}.

The substituents R^{10} may be selected such that they contain no more than 20 non-hydrogen atoms, for example, no more than 15 non-hydrogen atoms, e.g. no more than 12, or 10, or 9, or 8, or 7, or 6, or 5 non-hydrogen atoms.

Where the carbocyclic and heterocyclic groups have a pair of substituents on adjacent ring atoms, the two substituents may be linked so as to form a cyclic group. For example, an adjacent pair of substituents on adjacent carbon atoms of a ring may be linked via one or more heteroatoms and optionally substituted alkylene groups to form a fused oxa-, dioxa-, aza-, diaza- or oxa-aza-cycloalkyl group. Examples of such linked substituent groups include:



Examples of halogen substituents include fluorine, chlorine, bromine and iodine. Fluorine and chlorine are particularly preferred.

In the definition of the compounds of the formula (I) above and as used hereinafter, the term "hydrocarbyl" is a generic term encompassing aliphatic, alicyclic and aromatic groups having an all-carbon backbone, except where otherwise stated. In certain cases, as defined herein, one or more of the carbon atoms making up the carbon backbone may be replaced by a specified atom or group of atoms. Examples of hydrocarbyl groups include alkyl, cycloalkyl, cycloalkenyl, carbocyclic aryl, alkenyl, alkynyl, cycloalkylalkyl, cycloalkenylalkyl, and carbocyclic aralkyl, aralkenyl and aralkynyl groups. Such groups can be unsubstituted or, where stated, can be substituted by one or more substituents as defined herein. The examples and preferences expressed below

apply to each of the hydrocarbyl substituent groups or hydrocarbyl-containing substituent groups referred to in the various definitions of substituents for compounds of the formula (I) unless the context indicates otherwise.

Generally by way of example, the hydrocarbyl groups can have up to eight carbon atoms, unless the context requires otherwise. Within the sub-set of hydrocarbyl groups having 1 to 8 carbon atoms, particular examples are C_{1-6} hydrocarbyl groups, such as C_{1-4} hydrocarbyl groups (e.g. C_{1-3} hydrocarbyl groups or C_{1-2} hydrocarbyl groups), specific examples being any individual value or combination of values selected from C_1, C_2, C_3, C_4, C_5, C_6, C_7 and C_8 hydrocarbyl groups.

The term "alkyl" covers both straight chain and branched chain alkyl groups. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, 2-pentyl, 3-pentyl, 2-methyl butyl, 3-methyl butyl, and n-hexyl and its isomers. Within the sub-set of alkyl groups having 1 to 8 carbon atoms, particular examples are C_{1-6} alkyl groups, such as C_{1-4} alkyl groups (e.g. C_{1-3} alkyl groups or C_{1-2} alkyl groups).

Examples of cycloalkyl groups are those derived from cyclopropane, cyclobutane, cyclopentane, cyclohexane and cycloheptane. Within the sub-set of cycloalkyl groups the cycloalkyl group will have from 3 to 8 carbon atoms, particular examples being C_{3-6} cycloalkyl groups.

Examples of alkenyl groups include, but are not limited to, ethenyl (vinyl), 1-propenyl, 2-propenyl (allyl), isopropenyl, butenyl, buta-1,4-dienyl, pentenyl, and hexenyl. Within the sub-set of alkenyl groups the alkenyl group will have 2 to 8 carbon atoms, particular examples being C_{2-6} alkenyl groups, such as C_{2-4} alkenyl groups.

Examples of cycloalkenyl groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl and cyclohexenyl. Within the sub-set of cycloalkenyl groups the cycloalkenyl groups have from 3 to 8 carbon atoms, and particular examples are C_{3-6} cycloalkenyl groups.

Examples of alkynyl groups include, but are not limited to, ethynyl and 2-propynyl (propargyl) groups. Within the sub-set of alkynyl groups having 2 to 8 carbon atoms, particular examples are C_{2-6} alkynyl groups, such as C_{2-4} alkynyl groups.

Examples of carbocyclic aryl groups include substituted and unsubstituted phenyl, naphthyl, indane and indene groups.

Examples of cycloalkylalkyl, cycloalkenylalkyl, carbocyclic aralkyl, aralkenyl and aralkynyl groups include phenethyl, benzyl, styryl, phenylethynyl, cyclohexylmethyl, cyclopentylmethyl, cyclobutylmethyl, cyclopropylmethyl and cyclopentenylmethyl groups.

When present, and where stated, a hydrocarbyl group can be optionally substituted by one or more substituents selected from hydroxy, oxo, alkoxy, carboxy, halogen, cyano, nitro, amino, mono- or di-C_{1-4} hydrocarbylamino, and monocyclic or bicyclic carbocyclic and heterocyclic groups having from 3 to 12 (typically 3 to 10 and more usually 5 to 10) ring members. Preferred substituents include halogen such as fluorine. Thus, for example, the substituted hydrocarbyl group can be a partially fluorinated or perfluorinated group such as difluoromethyl or trifluoromethyl. In one embodiment preferred substituents include monocyclic carbocyclic and heterocyclic groups having 3-7 ring members.

Where stated, one or more carbon atoms of a hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$ wherein X^1 and X^2 are as hereinbefore defined. For example, 1, 2, 3 or 4 carbon atoms of the hydrocarbyl group may be replaced by one of the atoms or groups listed, and the replacing atoms or groups may be the same or different. Examples of groups in which a carbon atom of the hydrocarbyl group has been replaced by a replacement atom or group as defined above include ethers and thioethers (C replaced by O or S), amides, esters, thioamides and thioesters (C replaced by $X^1C(X^2)$ or $C(X^2)X^1$), sulphones and sulphoxides (C replaced by SO or SO_2) and amines (C replaced by NR^c).

Where an amino group has two hydrocarbyl substituents, they may, together with the nitrogen atom to which they are attached, and optionally with another heteroatom such as nitrogen, sulphur, or oxygen, link to form a ring structure of 4 to 7 ring members.

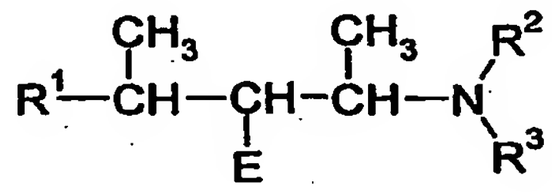
The definition "R^a-R^b" as used herein, either with regard to substituents present on a carbocyclic or heterocyclic moiety, or with regard to other substituents present at other locations on the compounds of the formula (I), includes *inter alia* compounds wherein R^a is selected from a bond, O, CO, OC(O), SC(O), $NR^cC(O)$, OC(S), SC(S), $NR^cC(S)$, $OC(NR^c)$, $SC(NR^c)$, $NR^cC(NR^c)$, C(O)O, C(O)S, $C(O)NR^c$, C(S)O, C(S)S, $C(S)NR^c$, $C(NR^c)O$, $C(NR^c)S$, $C(NR^c)NR^c$, OC(O)O, SC(O)O, $NR^cC(O)O$, OC(S)O, SC(S)O, $NR^cC(S)O$, $OC(NR^c)O$, $SC(NR^c)O$, $NR^cC(NR^c)O$, OC(O)S, SC(O)S, $NR^cC(O)S$, OC(S)S, SC(S)S, $NR^cC(S)S$, $OC(NR^c)S$, $SC(NR^c)S$, $NR^cC(NR^c)S$, $OC(O)NR^c$, $SC(O)NR^c$, $NR^cC(O)NR^c$, $OC(S)NR^c$, $SC(S)NR^c$, $NR^cC(S)NR^c$, $OC(NR^c)NR^c$, $SC(NR^c)NR^c$, $NR^cC(NR^c)NR^c$, S, SO, SO_2, NR^c, SO_2NR^c and NR^cSO_2 wherein R^c is as hereinbefore defined.

The moiety R^b can be hydrogen or it can be a group selected from carbocyclic and heterocyclic groups having from 3 to 12 ring members (typically 3 to 10 and more usually from 5 to 10), and a C_{1-8} hydrocarbyl group optionally substituted as hereinbefore defined. Examples of hydrocarbyl, carbocyclic and heterocyclic groups are as set out above.

<u>Specific Embodiments of and Preferences for A, E, R^1 to R^5 and R^9</u>

In formula (I), A is a saturated hydrocarbon linker group containing from 1 to 7 carbon atoms, the linker group having a maximum chain length of 5 atoms extending between R^1 and NR^2R^3 and a maximum chain length of 4 atoms extending between E and NR^2R^3. Within these constraints, the moieties E and R^1 can each be attached at any location on the group A.

The term "maximum chain length" as used herein refers to the number of atoms lying directly between the two moieties in question, and does not take into account any branching in the chain or any hydrogen atoms that may be present. For example, in the structure A shown below:



(A)

the chain length between R^1 and NR^2R^3 is 3 atoms whereas the chain length between E and NR^2R^3 is 2 atoms.

In general it is presently preferred that the linker group has a maximum chain length of 3 atoms (more preferably 1 or 2 atoms, and most preferably 2 atoms) extending between R^1 and NR^2R^3.

It is preferred that the linker group has a maximum chain length of 3 atoms extending between E and NR^2R^3.

In one particularly preferred group of compounds, the linker group has a chain length of 2 or 3 atoms extending between R^1 and NR^2R^3 and a chain length of 2 or 3 atoms extending between E and NR^2R^3.

One of the carbon atoms in the linker group may optionally be replaced by an oxygen or nitrogen atom, with nitrogen currently being preferred. When present, the nitrogen atom preferably is linked directly to the group E.

When a nitrogen atom or oxygen atom are present, it is preferred that the nitrogen or oxygen atom and the NR^2R^3 group are spaced apart by at least two intervening carbon atoms.

In one particular group of compounds within formula (I), the linker atom linked directly to the group E is a carbon atom and the linker group A has an all-carbon skeleton.

The carbon atoms of the linker group A may optionally bear one or more substituents selected from oxo, fluorine and hydroxy, provided that the hydroxy group is not located at a carbon atom α with respect to the NR^2R^3 group, and provided also that the oxo group is located at a carbon atom α with respect to the NR^2R^3 group. Typically, the hydroxy group, if present, is located at a position β with respect to the NR^2R^3 group. In general, no more than one hydroxy group will be present. Where fluorine atoms are present, they may be present in a difluoromethylene or trifluoromethyl group, for example.

It will be appreciated that that when an oxo group is present at the carbon atom adjacent the NR^2R^3 group, the compound of the formula (I) will be an amide.

In one embodiment of the invention, no fluorine atoms are present in the linker group A.

In another embodiment of the invention, no hydroxy groups are present in the linker group A.

In a further embodiment, no oxo group is present in the linker group A.

In one group of compounds of the formula (I) neither hydroxy groups nor fluorine atoms are present in the linker group A, e.g. the linker group A is unsubstituted.

Preferably, when a carbon atom in the linker group A is replaced by a nitrogen atom, the group A bears no more than one hydroxy substituent and more preferably bears no hydroxy substituents.

When there is a chain length of four atoms between E and NR^2R^3, it is preferred that the linker group A contains no nitrogen atoms and more preferably has an all carbon skeleton.

In order to modify the susceptibility of the compounds to metabolic degradation *in vivo*, the linker group A can have a branched configuration at the carbon atom attached to the NR^2R^3 group. For example, the carbon atom attached to the NR^2R^3 group can be attached to a pair of *gem*-dimethyl groups.

In one particular group of compounds of the formula (I), the portion R^1-A-NR^2R^3 of the compound is represented by the formula R^1-$(G)_k$-$(CH_2)_m$-X-$(CH_2)_n$-$(CR^6R^7)_p$-NR^2R^3 wherein G is NH, NMe or O; X is attached to the group E and is selected from $(CH_2)_j$-CH, $(CH_2)_j$-N and $(NH)_j$-CH; , j is 0 or 1, k is 0 or 1, m is 0 or 1, n is 0, 1, 2, or 3 and p is 0 or 1, and the sum of j, k, m, n and p does not exceed 4; and R^6 and R^7 are the same or different and are selected from methyl and ethyl, or CR^6R^7 forms a cyclopropyl group.

A preferred group CR^6R^7 is $C(CH_3)_2$.

Preferably X is $(CH_2)_j$-CH.

In one preferred configuration, k is 0, m is 0 or 1, n is 0, 1, 2 or 3 and p is 0.

In another preferred configuration, k is 0, m is 0 or 1, n is 0, 1 or 2 and p is 1.

In another configuration, X is $(CH_2)_j$-CH, k is 1, m is 0, n is 0, 1,2 or 3 and p is 0.

In another preferred configuration, X is $(CH_2)_j$-CH, k is 1, m is 0, n is 0, 1 or 2 and p is 1.

In a particularly preferred configuration, the portion R^1-A-NR^2R^3 of the compound is represented by the formula R^1-X-$(CH_2)_n$-NR^2R^3 wherein X is attached to the group E and is a group CH, and n is 2.

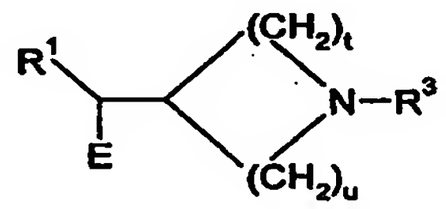
In one group of compounds of the invention, R^2 and R^3 are independently selected from hydrogen, C_{1-4} hydrocarbyl and C_{1-4} acyl. Typically the hydrocarbyl group is an alkyl group, more usually a C_1, C_2 or C_3 alkyl group, and preferably a methyl group. In a preferred sub-group of compounds, R^2 and R^3 are independently selected from hydrogen and methyl and hence NR^2R^3 can be an amino, methylamino or dimethylamino group. Most preferably, NR^2R^3 can be an amino group.

In another group of compounds, R^2 and R^3 together with the nitrogen atom to which they are attached form a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N.

The saturated monocyclic ring can be an azacycloalkyl group such as an azetidine, pyrrolidine, piperidine or azepane ring, and such rings are typically unsubstituted. Alternatively, the saturated monocyclic ring can contain an additional heteroatom selected from O and N, and examples of such groups include morpholine and piperazine. Where an additional N atom is present in the ring, this can form part of an NH group or an N-C_{1-4}alkyl group such as an N-methyl, N-ethyl, N-propyl or N-isopropyl group.

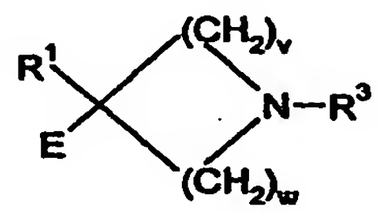
In a further group of compounds, one of R^2 and R^3 together with the nitrogen atom to which they are attached and one or more atoms from the linker group A form a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N.

Examples of such compounds include compounds wherein NR^2R^3 and A form a unit of the formula:



where t and u are each 0, 1, 2 or 3 provided that the sum of t and u falls within the range of 2 to 4.

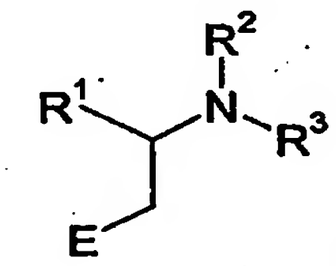
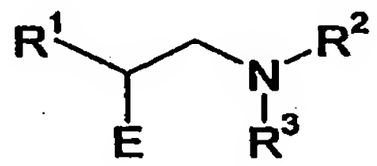
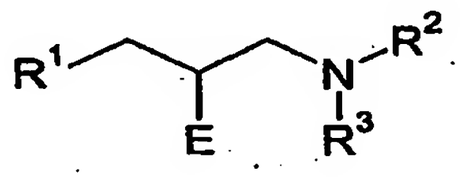
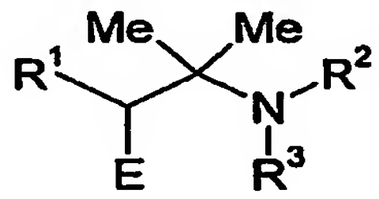
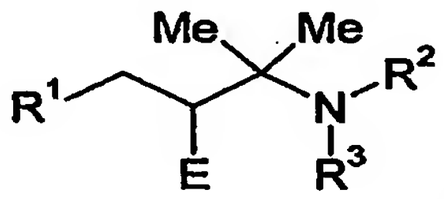
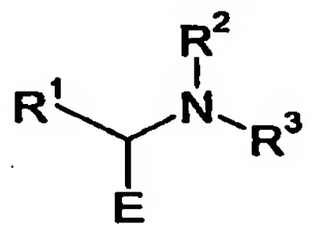
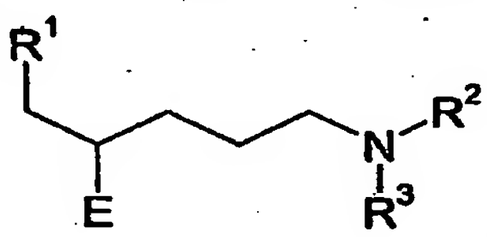
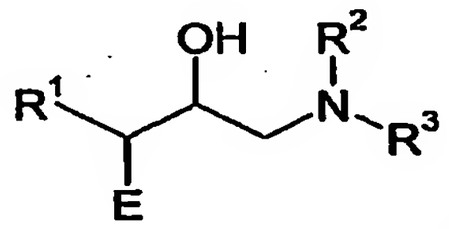
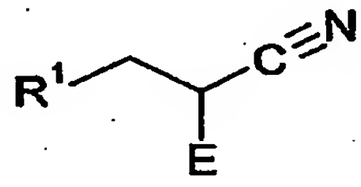
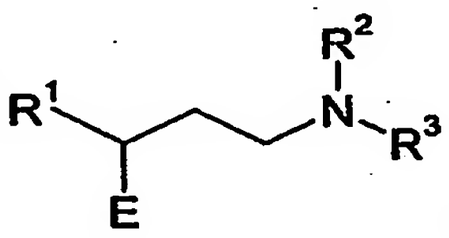
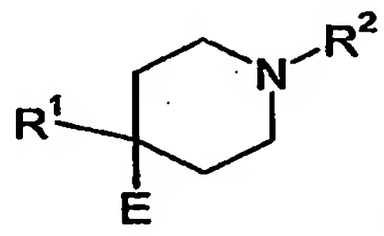
Further examples of such compounds include compounds wherein NR^2R^3 and A form a spiro-group of the formula:



where v and w are each 0, 1, 2 or 3 provided that the sum of v and w falls within the range of 2 to 5. Particular examples of spiro compounds are those in which v and w are both 2.

Particular examples of the linker group A, together with their points of attachment to the groups R^1, E and NR^2R^3, are shown in Table 1 below.

Table 1:

 A1	 A2	 A3
 A4	 A5	 A6
 A7	 A8	 A9
 A10	 A11	

Currently preferred groups include A1, A2, A3, A10 and A11. Particularly preferred groups include A2 and A11.

In formula (I), E is a monocyclic or bicyclic carbocyclic or heterocyclic group and can be selected from the groups set out above in the section headed General Preferences and Definitions.

Preferred groups E are monocyclic and bicyclic aryl and heteroaryl groups and, in particular, groups containing a six membered aromatic or heteroaromatic ring such as a phenyl, pyridine, pyrazine, pyridazine or pyrimidine ring, more particularly a phenyl, pyridine, pyrazine or pyrimidine ring, and more preferably a pyridine or phenyl ring.

Examples of bicyclic groups include benzo-fused and pyrido-fused groups wherein the group A and the pyrazole ring are both attached to the benzo- or pyrido- moiety.

In one embodiment, E is a monocyclic group.

Particular examples of monocyclic groups include monocyclic aryl and heteroaryl groups such as phenyl, thiophene, furan, pyrimidine, pyrazine and pyridine, phenyl being presently preferred.

Examples of non-aromatic monocyclic groups include cycloalkanes such as cylcohexane and cyclopentane, and nitrogen-containing rings such as piperazine and piperazone.

It is preferred that the group A and the pyrazole group are attached to the group E in a *meta* or *para* relative orientation; i.e. A and the pyrazole group are not attached to adjacent ring members of the group E. Examples of groups such groups E include 1,4-phenylene, 1,3-phenylene, 2,5-pyridylene and 2,4-pyridylene, 1,4-piperazinyl, and 1,4-piperazonyl.

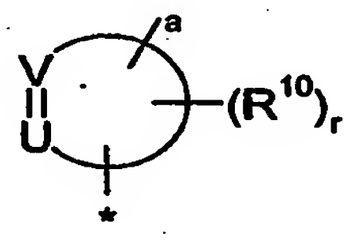
The groups E can be unsubstituted or can have up to 4 substituents R^8 which may be selected from the group R^{10} as hereinbefore defined. More typically however, the substituents R^8 are selected from hydroxy; oxo (when E is non-aromatic); halogen (e.g. chlorine and bromine); trifluoromethyl; cyano; C_{1-4} hydrocarbyloxy optionally substituted by C_{1-2} alkoxy or hydroxy; and C_{1-4} hydrocarbyl optionally substituted by C_{1-2} alkoxy or hydroxy.

Preferably there are 0-3 substituents, more preferably 0-2 substituents, for example 0 or 1 substituent. In one embodiment, the group E is unsubstituted.

E may be other than:

- a substituted pyridone group;
- a substituted thiazole group;
- a substituted or unsubstituted pyrazole or pyrazolone group;
- a substituted or unsubstituted bicyclic fused pyrazole group;
- a phenyl ring fused to a thiophene ring or a six membered nitrogen-containing heteroaryl ring fused to a thiophene ring;
- a substituted or unsubstituted piperazine group;

The group E can be an aryl or heteroaryl group having five or six members and containing up to three heteroatoms selected from O, N and S, the group E being represented by the formula:



where * denotes the point of attachment to the pyrazole group, and "a" denotes the attachment of the group A;

r is 0, 1 or 2;

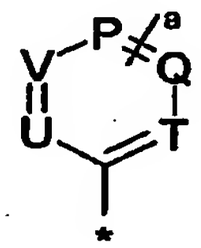
U is selected from N and CR^{12a}; and

V is selected from N and CR^{12b}; where R^{12a} and R^{12b} are the same or different and each is hydrogen or a substituent containing up to ten atoms selected from C, N, O, F, Cl and S provided that the total number of non-hydrogen atoms present in R^{12a} and R^{12b} together does not exceed ten;

or R^{12a} and R^{12b} together with the carbon atoms to which they are attached form an unsubstituted five or six membered saturated or unsaturated ring containing up to two heteroatoms selected from O and N; and

R^{10} is as hereinbefore defined.

In one preferred group of compounds, E is a group:



where * denotes the point of attachment to the pyrazole group, and "a" denotes the attachment of the group A;

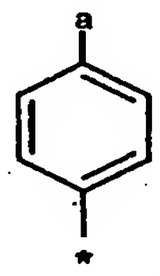
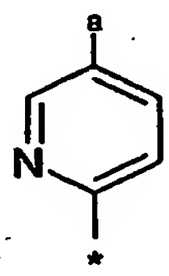
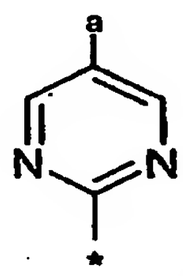
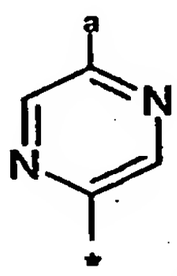
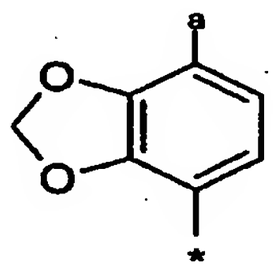
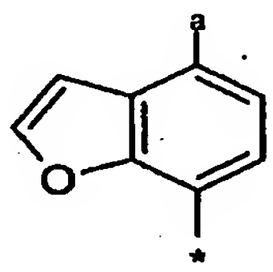
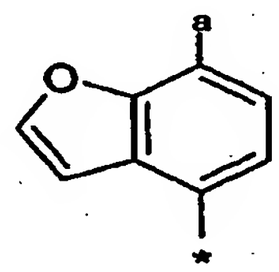
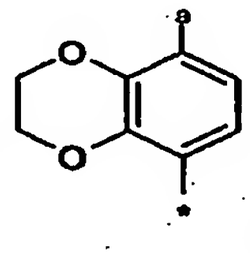
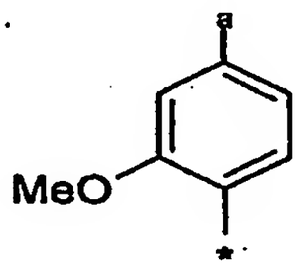
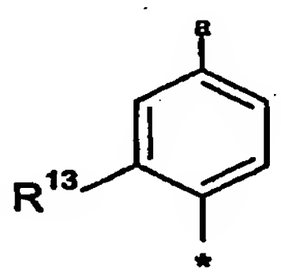
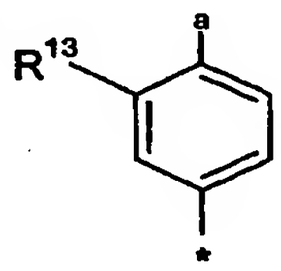
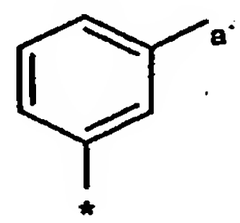
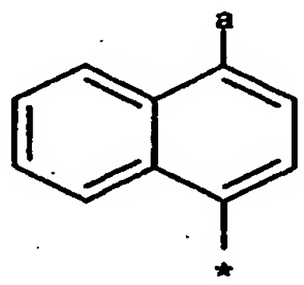
P, Q and T are the same or different and are selected from N, CH and NCR^{10}, provided that the group A is attached to a carbon atom; and U, V and R^{10} are as hereinbefore defined.

Examples of R^{12a} and R^{12b} include hydrogen and substituent groups R^{10} as hereinbefore defined having no more than ten non-hydrogen atoms. Particular examples of R^{12a} and R^{12b} include methyl, ethyl, propyl, isopropyl, cyclopropyl, cyclobutyl, cyclopentyl, fluorine, chlorine, methoxy, trifluoromethyl, hydroxymethyl, hydroxyethyl, methoxymethyl, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethyl, cyano, amino, methylamino, dimethylamino, $CONH_2$, CO_2Et, CO_2H, acetamido, azetidinyl, pyrrolidino, piperidine, piperazino, morpholino, methylsulphonyl, aminosulphonyl, mesylamino and trifluoroacetamido.

Preferably, when U is CR^{12a} and/or V is CR^{12b} the atoms or groups in R^{12a} and R^{12b} that are directly attached to the carbon atom ring members C are selected from H, O (e.g. as in methoxy), NH (e.g. as in amino and methylamino) and CH_2 (e.g. as in methyl and ethyl).

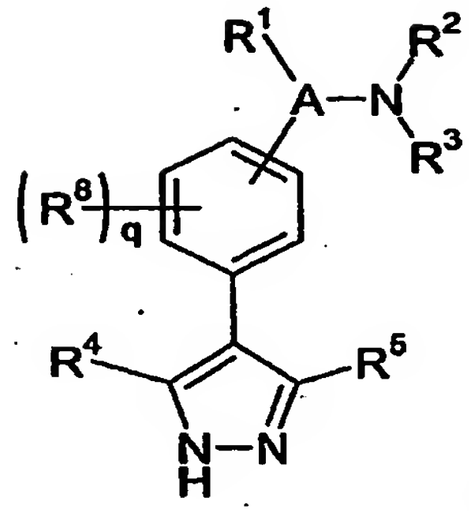
Particular examples of the linker group E, together with their points of attachment to the group A (^{a}) and the pyrazole ring (*) are shown in Table 2 below.

Table 2:

 B1	 B2	 B3	 B4
 B5	 B6	 B7	 B8
 B9	 B10	 B11	 B12
 B13			

In the table, the substituent group R^{13} is selected from methyl, chlorine, fluorine and trifluoromethyl.

One sub-group of compounds of the formula (I) has the general formula (II):



(II)

wherein the group A is attached to the *meta* or *para* position of the benzene ring, q is 0-4; R^1, R^2, R^3, R^4 and R^5 are as defined herein in respect of formula (I) and sub-groups, examples and preferences thereof; and R^8 is a substituent group as hereinbefore defined. In formula (II), q is preferably 0, 1 or 2, more preferably 0 or 1 and most preferably 0.

The group R^1 is an aryl or heteroaryl group and may be selected from the list of such groups set out in the section headed General Preferences and Definitions.

R^1 can be monocyclic or bicyclic and, in one preferred embodiment, is monocyclic. Particular examples of monocyclic aryl and heteroaryl groups are six membered aryl and heteroaryl groups containing up to 2 nitrogen ring members, and five membered heteroaryl groups containing up to 3 heteroatom ring members selected from O, S and N.

Examples of such groups include phenyl, naphthyl, thienyl, furan, pyrimidine and pyridine, with phenyl being presently preferred.

The group R^1 can be unsubstituted or substituted by up to 5 substituents, and examples of substituents are those listed in group R^{10} above. Preferred substituents include hydroxy; C_{1-4} acyloxy; fluorine; chlorine; bromine; trifluoromethyl; cyano; C_{1-4} hydrocarbyloxy and C_{1-4} hydrocarbyl each optionally substituted by C_{1-2} alkoxy or hydroxy; C_{1-4} acylamino; benzoylamino; pyrrolidinocarbonyl; piperidinocarbonyl; morpholinocarbonyl; piperazinocarbonyl; five and six membered heteroaryl groups containing one or

two heteroatoms selected from N, O and S, the heteroaryl groups being optionally substituted by one or more C_{1-4} alkyl substituents; phenyl; pyridyl; and phenoxy wherein the phenyl, pyridyl and phenoxy groups are each optionally substituted with 1, 2 or 3 substituents selected from C_{1-2} acyloxy, fluorine, chlorine, bromine, trifluoromethyl, cyano, C_{1-2} hydrocarbyloxy and C_{1-2} hydrocarbyl each optionally substituted by methoxy or hydroxy.

Although up to 5 substituents may be present, more typically there are 0, 1, 2, 3 or 4 substituents, preferably 0, 1, 2 or 3, and more preferably 0, 1 or 2.

In one embodiment, the group R^1 is unsubstituted or substituted by up to 5 substituents selected from hydroxy; C_{1-4} acyloxy; fluorine; chlorine; bromine; trifluoromethyl; cyano; C_{1-4} hydrocarbyloxy and C_{1-4} hydrocarbyl each optionally substituted by C_{1-2} alkoxy or hydroxy.

In another embodiment, the group R^1 can have one or two substituents selected from fluorine, chlorine, trifluoromethyl, methyl and methoxy. When R^1 is a phenyl group, particular examples of substituent combinations include mono-chlorophenyl and dichlorophenyl.

When R^1 is a six membered aryl or heteroaryl group, a substituent may advantageously be present at the *para* position on the six-membered ring. Where a substituent is present at the *para* position, it is preferably larger in size than a fluorine atom.

In formula (I), R^4 is selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, cyano and CF_3. Preferred values for R^4 include hydrogen and methyl.

In formula (I), R^5 is selected from selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, cyano, $CONH_2$, $CONHR^9$, CF_3, NH_2, $NHCOR^9$ and $NHCONHR^9$ where R^9 is optionally substituted phenyl or benzyl.

More preferably, R^5 is selected from selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, cyano, CF_3, NH_2, $NHCOR^9$ and $NHCONHR^9$ where R^9 is optionally substituted phenyl or benzyl.

The group R^9 is typically unsubstituted phenyl or benzyl, or phenyl or benzyl substituted by 1,2 or 3 substituents selected from halogen; hydroxy; trifluoromethyl; cyano; carboxy; C_{1-4}alkoxycarbonyl; C_{1-4} acyloxy; amino; mono- or di-C_{1-4} alkylamino; C_{1-4} alkyl optionally substituted by halogen, hydroxy or C_{1-2} alkoxy; C_{1-4} alkoxy optionally substituted by halogen, hydroxy or C_{1-2} alkoxy; phenyl, five and six membered heteroaryl groups containing up to 3 heteroatoms selected from O, N and S; and saturated carbocyclic and heterocyclic groups containing up to 2 heteroatoms selected from O, S and N.

Particular examples of the moiety R^5 include hydrogen, fluorine, chlorine, bromine, methyl, ethyl, hydroxyethyl, methoxymethyl, cyano, CF_3, NH_2, $NHCOR^{9a}$ and $NHCONHR^{9a}$ where R^{9a} is phenyl or benzyl optionally substituted by hydroxy, C_{1-4} acyloxy, fluorine, chlorine, bromine, trifluoromethyl, cyano, C_{1-4} hydrocarbyloxy (e.g. alkoxy) and C_{1-4} hydrocarbyl (e.g. alkyl) optionally substituted by C_{1-2} alkoxy or hydroxy.

In another sub-group of compounds of the invention, A is a saturated hydrocarbon linker group containing from 1 to 7 carbon atoms, the linker group having a maximum chain length of 5 atoms extending between R^1 and NR^2R^3 and a maximum chain length of 4 atoms extending between E and NR^2R^3, wherein one of the carbon atoms in the linker group may optionally be replaced by an oxygen or nitrogen atom; and wherein the carbon atoms of the linker group A may optionally bear one or more substituents selected from fluorine and hydroxy, provided that the hydroxy group when present is not located at a carbon atom α with respect to the NR^2R^3 group; and

R^5 is selected from selected from hydrogen, C_{1-5} saturated hydrocarbyl, cyano, $CONH_2$, CF_3, NH_2, $NHCOR^9$ and $NHCONHR^9$.

For the avoidance of doubt, it is to be understood that each general and specific preference, embodiment and example of the groups R^1 may be combined with each general and specific preference, embodiment and example of the groups R^2 and/or R^3 and/or R^4 and/or R^5 and/or R^9 and that all such combinations are embraced by this application.

The various functional groups and substituents making up the compounds of the formula (I) are typically chosen such that the molecular weight of the compound of the formula (I) does not exceed 1000. More usually, the molecular weight of the compound will be less than 750, for example less than 700, or less than 650, or less than 600, or less than 550. More preferably, the molecular weight is less than 525 and, for example, is 500 or less.

Particular compounds of the invention are as illustrated in the examples below.

In one embodiment, the compound of the formula (I) is selected from the group consisting of:

{2-(4-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-methyl-amine (R);
4-(4-chloro-phenyl)-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine;
3-(4-chloro-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propylamine;
3-(3,4-dichloro-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propylamine;
{3-(4-chloro-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-methyl-amine;
{2-(4-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-dimethyl-amine; and
2-(4-chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethylamine.

Many compounds of the formula (I) can exist in the form of salts, for example acid addition salts or, in certain cases salts of organic and inorganic bases such as carboxylate, sulphonate and phosphate salts. All such salts are within the scope of this invention, and references to compounds of the formula (I) include the salt forms of the compounds.

Acid addition salts may be formed with a wide variety of acids, both inorganic and organic. Examples of acid addition salts include salts formed with hydrochloric, hydriodic, phosphoric, nitric, sulphuric, citric, lactic, succinic, maleic, malic, isethionic, fumaric, benzenesulphonic, toluenesulphonic, methanesulphonic, ethanesulphonic, naphthalenesulphonic, valeric, acetic, propanoic, butanoic, malonic, glucuronic and lactobionic acids.

If the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be -COO^-), then a salt may be formed with a suitable cation.

Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^+ and K^+, alkaline earth cations such as Ca^{2+} and Mg^{2+}, and other cations such as Al^{3+}. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^+) and substituted ammonium ions (e.g., NH_3R^+, $NH_2R_2^+$, NHR_3^+, NR_4^+). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $N(CH_3)_4^+$.

Where the compounds of the formula (I) contain an amine function, these may form quaternary ammonium salts, for example by reaction with an alkylating agent according to methods well known to the skilled person. Such quaternary ammonium compounds are within the scope of formula (I).

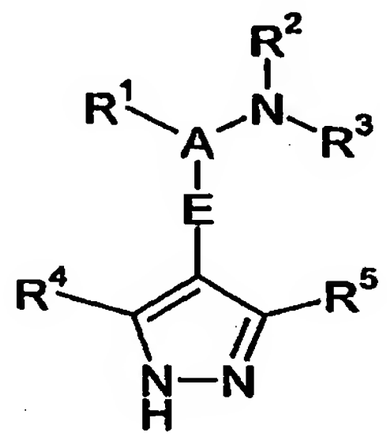
Compounds of the formula (I) containing an amine function may also form N-oxides. A reference herein to a compound of the formula (I) that contains an amine function also includes the N-oxide.

Where a compound contains several amine functions, one or more than one nitrogen atom may be oxidised to form an N-oxide. Particular examples of N-oxides are the N-oxides of a tertiary amine or a nitrogen atom of a nitrogen-containing heterocycle.

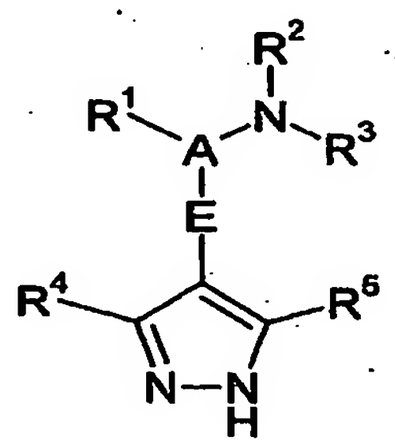
N-Oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as hydrogen peroxide or a per-acid (e.g. a peroxycarboxylic acid), see for example *Advanced Organic Chemistry*, by Jerry March, 4th Edition, Wiley Interscience, pages. More particularly, N-oxides can be made by the procedure of L. W. Deady (*Syn. Comm.* 1977, 7, 509-514) in which the amine compound is reacted with *m*-chloroperoxybenzoic acid (MCPBA), for example, in an inert solvent such as dichloromethane.

Compounds of the formula (I) may exist in a number of different geometric isomeric, and tautomeric forms and references to compounds of the formula (I) include all such forms. For the avoidance of doubt, where a compound can exist in one of several geometric isomeric or tautomeric forms and only one is specifically described or shown, all others are nevertheless embraced by formula (I).

For example, in compounds of the formula (I) the pyrazole group may take either of the following two tautomeric forms A and B.



A



B

For simplicity, the general formula (I) illustrates form A but the formula is to be taken as embracing both form A and form B.

Where compounds of the formula (I) contain one or more chiral centres, and can exist in the form of two or more optical isomers, references to compounds of the formula (I) include all optical isomeric forms thereof (e.g. enantiomers and diastereoisomers), either as individual optical isomers, or mixtures or two or more optical isomers, unless the context requires otherwise.

For example, the group A can include one or more chiral centres. Thus, when E and R^1 are both attached to the same carbon atom on the linker group A; the said carbon atom is typically chiral and hence the compound of the formula (I) will exist as a pair of enantiomers (or more than one pair of enantiomers where more than one chiral centre is present in the compound).

The optical isomers may be characterised and identified by their optical activity (i.e. as + and – isomers) or they may be characterised in terms of their absolute stereochemistry using the "R and S" nomenclature developed by Cahn, Ingold and Prelog, see *Advanced Organic Chemistry* by Jerry March, 4th Edition, John Wiley & Sons, New York, 1992, pages 109-114, and see also Cahn, Ingold & Prelog, *Angew. Chem. Int. Ed. Engl.*, 1966, 5, 385-415.

Optical isomers can be separated by a number of techniques including chiral chromatography (chromatography on a chiral support) and such techniques are well known to the person skilled in the art.

Where compounds of the formula (I) exist as two or more optical isomeric forms, one enantiomer in a pair of enantiomers may exhibit advantages over the other enantiomer, for example, in terms of biological activity. Thus, in certain circumstances, it may be desirable to use as a therapeutic agent only one of a pair of enantiomers, or only one of a plurality of diastereoisomers. Accordingly, the invention provides compositions containing a compound of the formula (I) having one or more chiral centres, wherein at least 55% (e.g. at least 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95%) of the compound of the formula (I) is present as a single optical isomer (e.g. enantiomer or diastereoisomer). In one general embodiment, 99% or more (e.g. substantially all) of the total amount of the compound of the formula (I) may be present as a single optical isomer (e.g. enantiomer or diastereoisomer).

Esters such as carboxylic acid esters and acyloxy esters of the compounds of formula (I) bearing a carboxylic acid group or a hydroxyl group are also embraced by Formula (I). Examples of esters are compounds containing the group -C(=O)OR, wherein R is an ester substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Particular examples of ester groups include, but are not limited to, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, $-C(=O)OC(CH_3)_3$, and -C(=O)OPh. Examples of acyloxy (reverse ester) groups are represented by -OC(=O)R, wherein R is an acyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or

a C_{5-20} aryl group, preferably a C_{1-7}alkyl group. Particular examples of acyloxy groups include, but are not limited to, -OC(=O)CH_3 (acetoxy), -OC(=O)CH_2CH_3, -OC(=O)$C(CH_3)_3$, -OC(=O)Ph, and -OC(=O)CH_2Ph.

Also encompassed by formula (I) are any polymorphic forms of the compounds, solvates (e.g. hydrates), complexes (e.g. inclusion complexes or clathrates with compounds such as cyclodextrins, or complexes with metals) of the compounds, and pro-drugs of the compounds. By "prodrugs" is meant for example any compound that is converted *in vivo* into a biologically active compound of the formula (I).

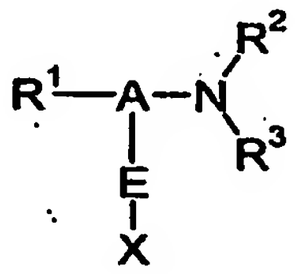
For example, some prodrugs are esters of the active compound (e.g., a physiologically acceptable metabolically labile ester). During metabolism, the ester group (-C(=O)OR) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any of the carboxylic acid groups (-C(=O)OH) in the parent compound, with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required.

Examples of such metabolically labile esters include those of the formula -C(=O)OR wherein R is:
C_{1-7}alkyl (e.g., -Me, -Et, -nPr, -iPr, -nBu, -sBu, -iBu, -tBu);
C_{1-7} aminoalkyl (e.g., aminoethyl; 2-(N,N-diethylamino)ethyl; 2-(4-morpholino)ethyl); and
acyloxy-C_{1-7}alkyl (e.g., acyloxymethyl; acyloxyethyl; pivaloyloxymethyl; acetoxymethyl; 1-acetoxyethyl; 1-(1-methoxy-1-methyl)ethyl-carbonyloxyethyl; 1-(benzoyloxy)ethyl; isopropoxy-carbonyloxymethyl; 1-isopropoxy-carbonyloxyethyl; cyclohexyl-carbonyloxymethyl; 1-cyclohexyl-carbonyloxyethyl; cyclohexyloxy-carbonyloxymethyl; 1-cyclohexyloxy-carbonyloxyethyl; (4-tetrahydropyranyloxy) carbonyloxymethyl; 1-(4-tetrahydropyranyloxy)-carbonyloxyethyl; (4-tetrahydropyranyl)carbonyloxymethyl; and 1-(4-tetrahydropyranyl)-carbonyloxyethyl).

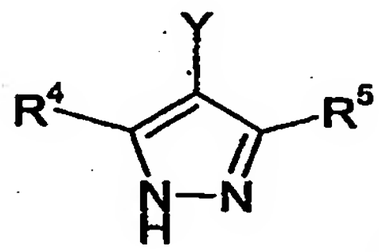
Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound (for example, as in antigen-directed enzyme pro-drug therapy (ADEPT), gene-directed enzyme pro-drug therapy (GDEPT) and ligand-directed enzyme pro-drug therapy (LIDEPT). For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

Methods for the preparation of compounds of the formula (I)

Compounds of the formula (I) can be prepared by reaction of a compound of the formula (X) with a compound of the formula (XI) or an N-protected derivative thereof:



(X)



(XI)

wherein A, E, and R^1 to R^5 are as hereinbefore defined, one of the groups X and Y is chlorine, bromine or iodine or a trifluoromethanesulphonate (triflate) group, and the other one of the groups X and Y is a boronate residue, for example a boronate ester or boronic acid residue.

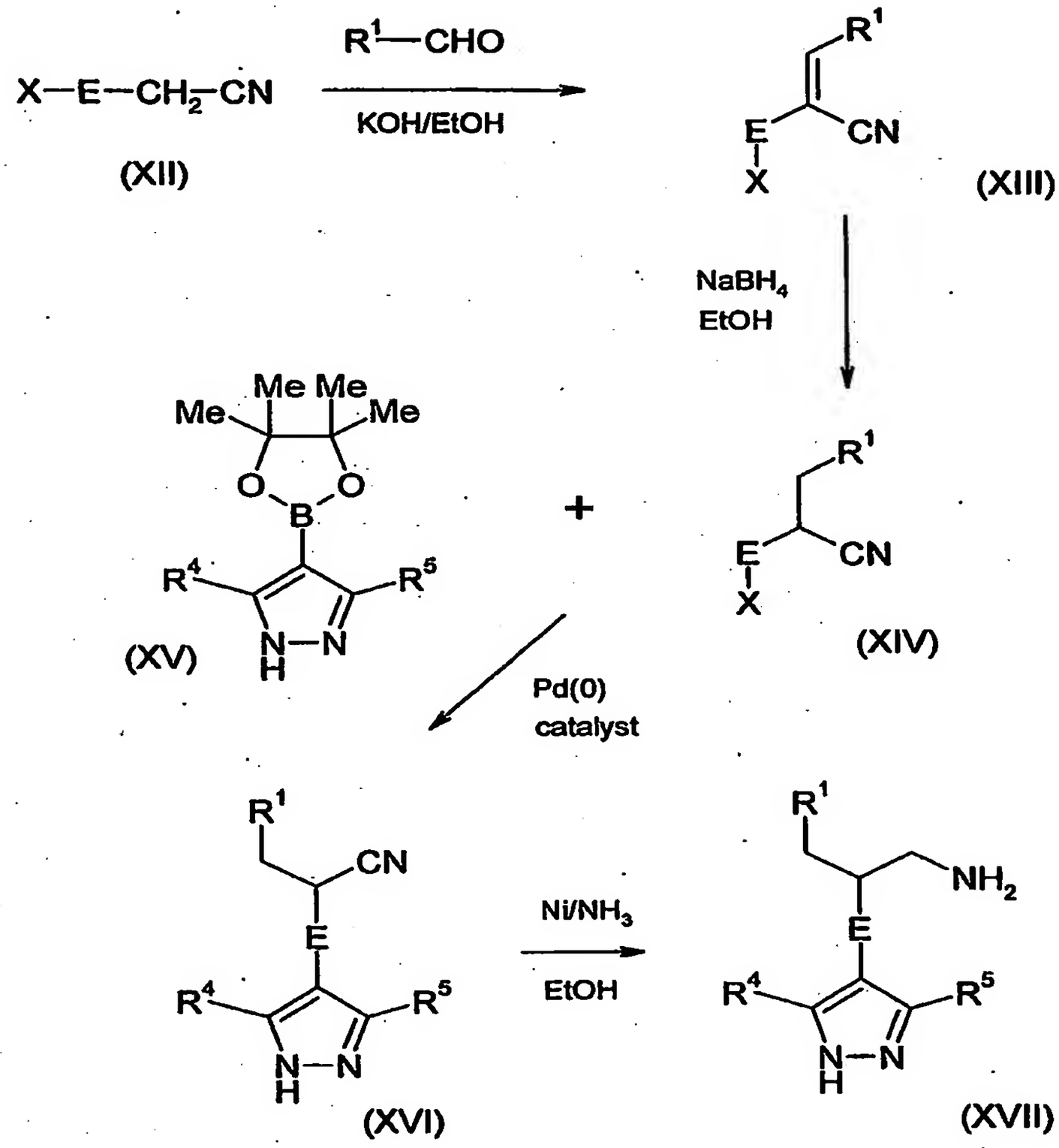
The reaction can be carried out under typical Suzuki Coupling conditions in the presence of a palladium catalyst such as bis(tri-*t*-butylphosphine)palladium and a base (e.g. a carbonate such as potassium carbonate). The reaction may be carried out in an aqueous solvent system, for example aqueous ethanol, and the reaction mixture is typically subjected to heating, for example to a temperature in excess of 100°C.

An illustrative synthetic route involving a Suzuki coupling step is shown in Scheme 1. The starting material for the synthetic route shown in scheme 1 is the halo-substituted aryl- or heteroarylmethyl nitrile (XII) in which X is a chlorine, bromine or iodine atom or a triflate group. The nitrile (XII) is condensed with the

aldehyde R^1CHO in the presence of an alkali such as sodium or potassium hydroxide in an aqueous solvent system such as aqueous ethanol. The reaction can be carried out at room temperature.

The resulting substituted acrylonitrile derivative (XIII) is then treated with a reducing agent that will selectively reduce the alkene double bond without reducing the nitrile group. A borohydride such as sodium borohydride may be used for this purpose to give the substituted acetonitrile derivative (XIV). The reduction reaction is typically carried out in a solvent such as ethanol and usually with heating, for example to a temperature up to about 65°C.

The reduced nitrile (XIV) is then coupled with the pyrazole boronate ester (XV) under the Suzuki coupling conditions described above to give a compound of the formula (I) in which $A\text{-}NR^2R^3$ is a substituted acetonitrile group.



Scheme 1

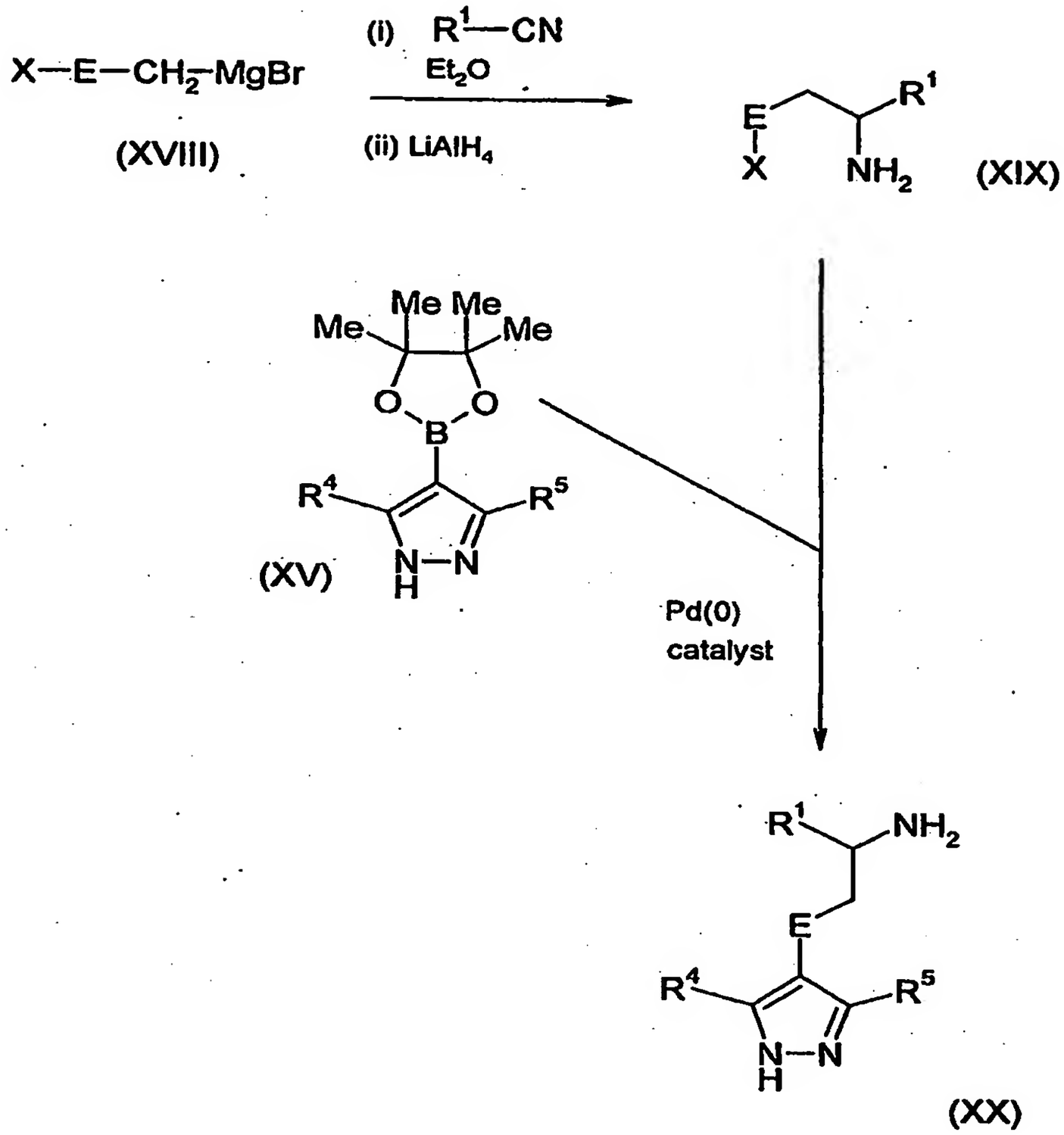
The substituted acetonitrile compound (XVI) may then be reduced to the corresponding amine (XVII) by treatment with a suitable reducing agent such as Raney nickel and ammonia in ethanol.

The synthetic route shown in Scheme 1 gives rise to amino compounds of the formula (I) in which the aryl or heteroaryl group E is attached to the β-position of the group A relative to the amino group. In order to give amino compounds of the formula (I) in which R^1 is attached to the β-position relative to the amino group,

the functional groups on the two starting materials in the condensation step can be reversed so that a compound of the formula X-E-CHO wherein X is bromine, chlorine, iodine or a triflate group is condensed with a compound of the formula R^1-CH_2-CN to give a substituted acrylonitrile derivative which is then reduced to the corresponding acetonitrile derivative before coupling with the pyrazole boronate (XV) and reducing the cyano group to an amino group.

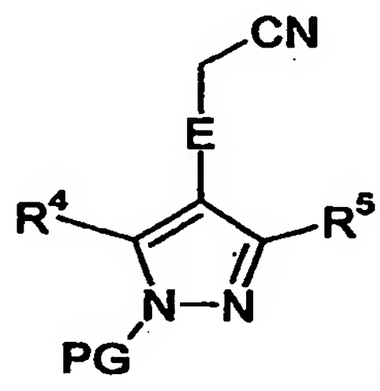
Compounds of the formula (I) in which R^1 is attached to the α-position relative to the amino group can be prepared by the sequence of reactions shown in Scheme 2.

In Scheme 2, the starting material is a halo-substituted aryl- or heteroarylmethyl Grignard reagent (XVIII, X = bromine or chlorine) which is reacted with the nitrile R^1-CN in a dry ether such as diethyl ether to give an intermediate imine (not shown) which is reduced to give the amine (XIX) using a reducing agent such as lithium aluminium hydride. The amine (XIX) can be reacted with the boronate ester (XV) under the Suzuki coupling conditions described above to yield the amine (XX).



Scheme 2

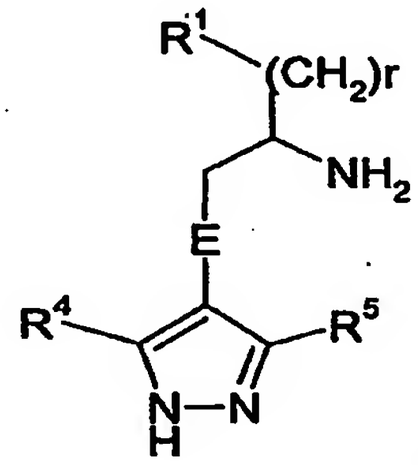
Compounds of the formula (I) can also be prepared from the substituted nitrile compound (XXI):



(XXI)

wherein PG is a protecting group such as a tetrahydropyranyl group. The nitrile (XXI) can be condensed with an aldehyde of the formula R^1-$(CH_2)_r$-CHO, wherein r is 0 or 1, and the resulting substituted acrylonitrile subsequently reduced to the corresponding substituted nitrile under conditions analogous to those set out in Scheme 1 above. The protecting group PG can then be removed by an appropriate method. The nitrile compound may subsequently be reduced to the corresponding amine by the use of a suitable reducing agent as described above.

The nitrile compound (XXI) may also be reacted with a Grignard reagent of the formula R^1-$(CH_2)_r$-MgBr under standard Grignard reaction conditions followed by deprotection to give an amino compound of the invention which has the structure shown in formula (XXII).

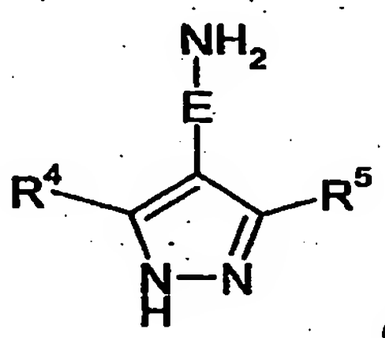


(XXII)

In the preparative procedures outlined above, the coupling of the aryl or heteroaryl group E to the pyrazole is accomplished by reacting a halo-pyrazole or halo-aryl or heteroaryl compound with a boronate ester or boronic acid in the presence of a palladium catalyst and base. Many boronates suitable for use in preparing compounds of the invention are commercially available, for example from Boron Molecular Limited of Noble Park, Australia, or from Combi-Blocks Inc, of San Diego, USA. Where the boronates are not commercially available, they can be prepared by methods known in the art, for example as described in the review article by N. Miyaura and A. Suzuki, *Chem. Rev.* 1995, *95*, 2457. Thus, boronates can be prepared by reacting the corresponding bromo-compound with an alkyl

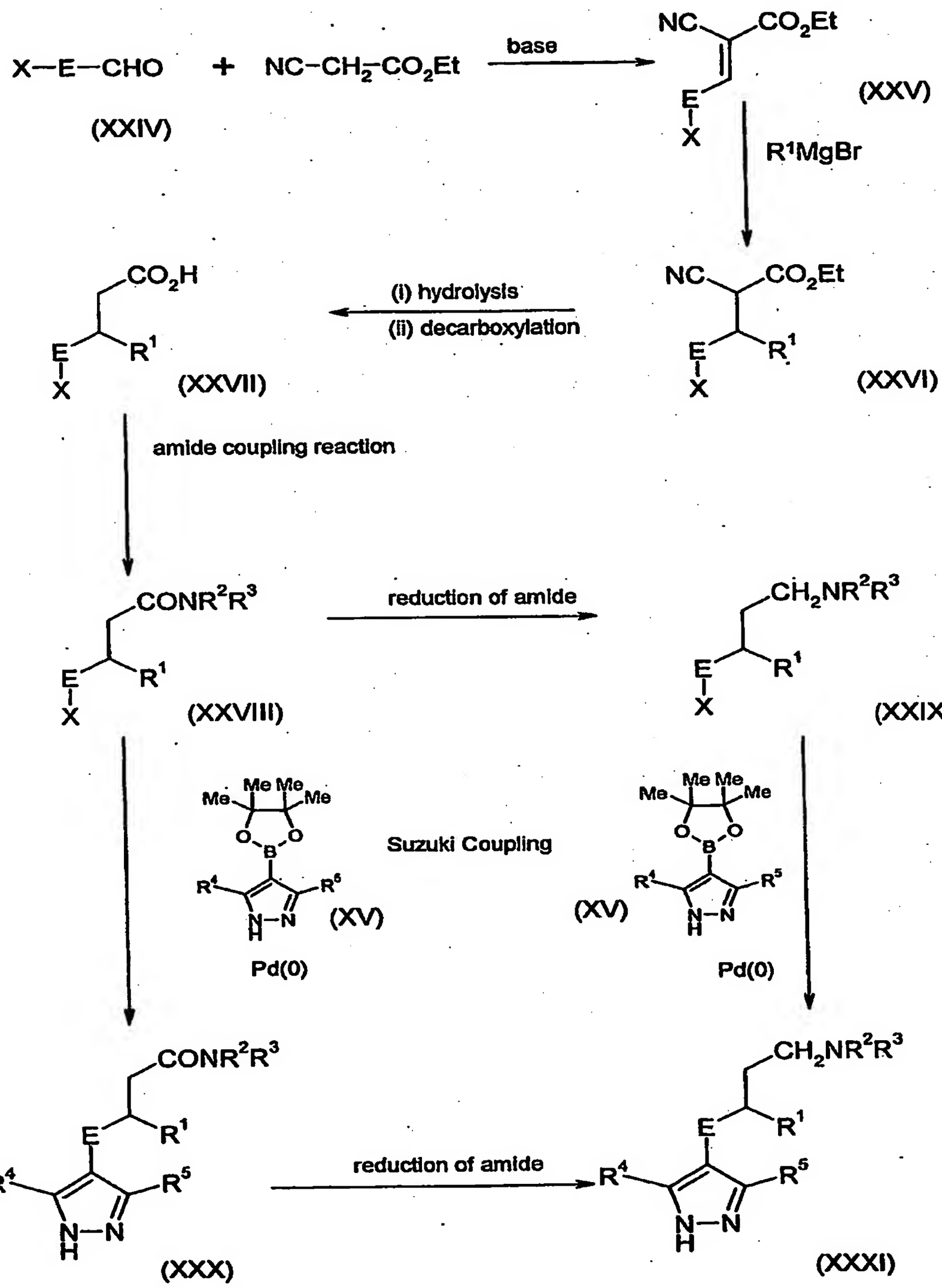
lithium such as butyl lithium and then reacting with a borate ester. The resulting boronate ester derivative can, if desired, be hydrolysed to give the corresponding boronic acid.

Compounds of the formula (I) in which the group A contains a nitrogen atom attached to the group E can be prepared by well known synthetic procedures from compounds of the formula (XXIII) or a protected form thereof. Compounds of the formula (XXIII) can be obtained by a Suzuki coupling reaction of a compound of the formula (XV) (see Scheme 1) with a compound of the formula Br-E-NH_2 such as 4-bromoaniline.



(XXIII)

Compounds of the formula (I) in which R^1 and E are connected to the same carbon atom can be prepared as shown in Scheme 3.



Scheme 3

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In Scheme 3, an aldehyde compound (XXIV) where X is bromine, chlorine, iodine or a triflate group is condensed with ethyl cyanoacetate in the presence of a base to give a cyanoacrylate ester intermediate (XXV). The condensation is typically carried out in the presence of a base, preferably a non-hydroxide such as piperidine, by heating under Dean Stark conditions.

The cyanoacrylate intermediate (XXV) is then reacted with a Grignard reagent R^1MgBr suitable for introducing the group R^1 by Michael addition to the carbon-carbon double bond of the acrylate moiety. The Grignard reaction may be carried out in a polar non-protic solvent such as tetrahydrofuran at a low temperature, for example at around 0 °C. The product of the Grignard reaction is the cyano propionic acid ester (XXVI) and this is subjected to hydrolysis and decarboxylation to give the propionic acid derivative (XXVII). The hydrolysis and decarboxylation steps can be effected by heating in an acidic medium, for example a mixture of sulphuric acid and acetic acid.

The propionic acid derivative (XXVII) is converted to the amide (XXVIII) by reaction with an amine HNR^2R^3 under conditions suitable for forming an amide bond. The coupling reaction between the propionic acid derivative (XXVII) and the amine HNR^2R^3 is preferably carried out in the presence of a reagent of the type commonly used in the formation of peptide linkages. Examples of such reagents include 1,3-dicyclohexylcarbodiimide (DCC) (Sheehan *et al*, *J. Amer. Chem Soc.* 1955, 77, 1067), 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide (referred to herein either as EDC or EDAC) (Sheehan *et al, J. Org. Chem., 1961, 26, 2525*), uronium-based coupling agents such as *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) and phosphonium-based coupling agents such as 1-benzo-triazolyloxytris-(pyrrolidino)phosphonium hexafluorophosphate (PyBOP) (Castro *et al, Tetrahedron Letters*, 1990, 31, 205). Carbodiimide-based coupling agents are advantageously used in combination with 1-hydroxy-7-azabenzotriazole (HOAt) (L. A. Carpino, *J. Amer. Chem. Soc.*, 1993, 115, 4397) or 1-hydroxybenzotriazole (HOBt) (Konig *et al*, *Chem. Ber.*, 103, 708, 2024-2034). Preferred coupling reagents include EDC (EDAC) and DCC in combination with HOAt or HOBt.

The coupling reaction is typically carried out in a non-aqueous, non-protic solvent such as acetonitrile, dioxan, dimethylsulphoxide, dichloromethane, dimethylformamide or N-methylpyrrolidine, or in an aqueous solvent optionally together with one or more miscible co-solvents. The reaction can be carried out at room temperature or, where the reactants are less reactive (for example in the case of electron-poor anilines bearing electron withdrawing groups such as sulphonamide groups) at an appropriately elevated temperature. The reaction may be carried out in the presence of a non-interfering base, for example a tertiary amine such as triethylamine or *N,N*-diisopropylethylamine.

Where the amine HNR^2R^3 is ammonia, the amide coupling reaction can be carried out using 1,1'-carbonyldiimidazole (CDI) to activate the carboxylic acid before addition of the ammonia.

As an alternative, a reactive derivative of the carboxylic acid, e.g. an anhydride or acid chloride, may be used. Reaction with a reactive derivative such an anhydride is typically accomplished by stirring the amine and anhydride at room temperature in the presence of a base such as pyridine.

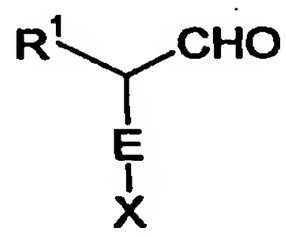
The amide (XXVIII) can be converted to a compound of the formula (XXX) (which corresponds to a compound of the formula (I) wherein A has an oxo substituent next to the NR^2R^3 group) by reaction with a boronate (XV) under Suzuki coupling conditions as described above. The amide (XXX) can subsequently be reduced using a hydride reducing agent such as lithium aluminium hydride in the presence of aluminium chloride to give an amine of the formula (XXXI) (which corresponds to a compound of the formula (I) wherein A is $CH\text{-}CH_2\text{-}CH_2$-). The reduction reaction is typically carried out in an ether solvent, for example diethyl ether, with heating to the reflux temperature of the solvent.

Rather than reacting the amide (XXVIII) with the boronate (XV), the amide may instead be reduced with lithium aluminium hydride/aluminium chloride, for

example in an ether solvent at ambient temperature, to give the amine (XXIX) which is then reacted with the boronate (XV) under the Suzuki coupling conditions described above to give the amine (XXX).

In order to obtain the homologue of the amine (XXIX) containing one fewer methylene group, the carboxylic acid (XXVII) can be converted to the azide by standard methods and subjected to a Curtius rearrangement (see *Advanced Organic Chemistry*, 4th edition, by Jerry March, John Wiley & sons, 1992, pages 1091-1092.

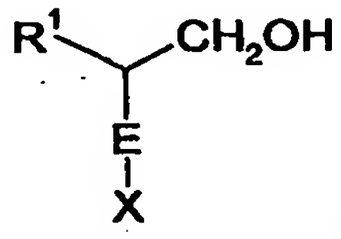
Intermediate compounds of the formula (X) where the moiety X is a chlorine, bromine or iodine atom and A is a group CH-CH_2- can be prepared by the reductive amination of an aldehyde compound of the formula (XXXII):



(XXXII)

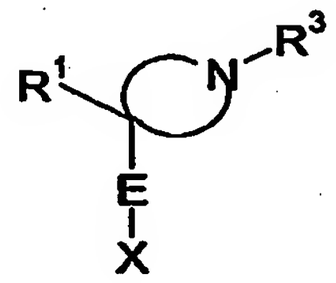
with an amine of the formula HNR^2R^3 under standard reductive amination conditions, for example in the presence of sodium cyanoborohydride in an alcohol solvent such as methanol or ethanol.

The aldehyde compound (XXXII) can be obtained by oxidation of the corresponding alcohol (XXXIII) using, for example, the Dess-Martin periodinane (see Dess, D.B.; Martin, J.C. *J. Org. Soc.*, 1983, *48*, 4155 and *Organic Syntheses*, Vol. 77, 141).



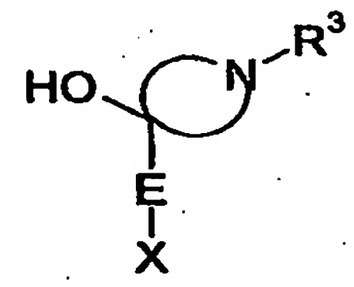
(XXXIII)

Compounds of the formula (I) where A, N and R^2 together form a spirocyclic group can be formed by the Suzuki coupling of a boronate compound of the formula (XV) with a spirocyclic intermediate of the formula (XXXIV) or an N-protected derivative thereof.



(XXXIV)

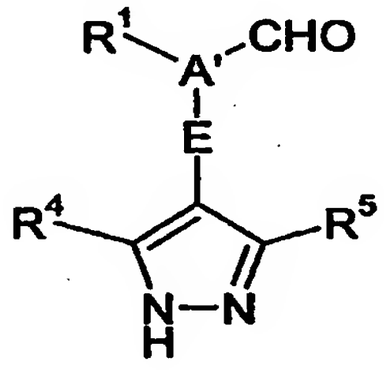
Spirocyclic intermediates of the formula (XXXIV) where R^1 is an aryl group such as an optionally substituted phenyl group, can be formed by Friedel Crafts alkylation of an aryl compound R^1-H with a compound of the formula (XXXV):



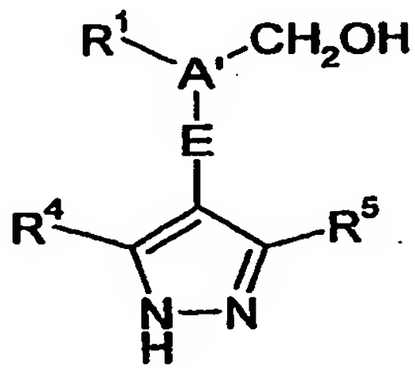
(XXXV)

The alkylation is typically carried out in the presence of a Lewis acid such as aluminium chloride at a reduced temperature, for example less than 5 °C.

In a further method for the preparation of a compound of the formula (I) wherein the moiety NR^2R^3 is attached to a CH_2 group of the moiety A, an aldehyde of the formula (XXXVI) can be coupled with an amine of the formula HNR^2R^3 under reductive amination conditions as described above. In the formulae (XXXVI) and (XXXVII), A' is the residue of the group A – i.e. the moieties A' and CH_2 together form the group A. The aldehyde (XXXVII) can be formed by oxidation of the corresponding alcohol using, for example, Dess-Martin periodinane.



(XXXVI)



(XXXVII)

Once formed, many compounds of the formula (I) can be converted into other compounds of the formula (I) using standard functional group interconversions.

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For example, compounds of the formula (I) in which the NR^2R^3 forms part of a nitrile group can be reduced to the corresponding amine. Compounds in which NR^2R^3 is an NH_2 group can be converted to the corresponding alkylamine by reductive alkylation, or to a cyclic group. Examples of functional group interconversions and reagents and conditions for carrying out such conversions can be found in, for example, *Advanced Organic Chemistry*, by Jerry March, 4th edition, 119, Wiley Interscience, New York, *Fiesers' Reagents for Organic Synthesis*, Volumes 1-17, John Wiley, edited by Mary Fieser (ISBN: 0-471-58283-2), and *Organic Syntheses*, Volumes 1-8, John Wiley, edited by Jeremiah P. Freeman (ISBN: 0-471-31192-8).

In many of the reactions described above, it may be necessary to protect one or more groups to prevent reaction from taking place at an undesirable location on the molecule. Examples of protecting groups, and methods of protecting and deprotecting functional groups, can be found in *Protective Groups in Organic Synthesis* (T. Green and P. Wuts; 3rd Edition; John Wiley and Sons, 1999).

A hydroxy group may be protected, for example, as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH_3, -OAc). An aldehyde or ketone group may be protected, for example, as an acetal (R-$CH(OR)_2$) or ketal ($R_2C(OR)_2$), respectively, in which the carbonyl group (>C=O) is converted to a diether (>$C(OR)_2$), by reaction with, for example, a primary alcohol. The aldehyde or ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid. An amine group may be protected, for example, as an amide (-NRCO-R) or a urethane (-NRCO-OR), for example, as: a methyl amide (-NHCO-CH_3); a benzyloxy amide (-NHCO-$OCH_2C_6H_5$, -NH-Cbz); as a t-butoxy amide (-NHCO-$OC(CH_3)_3$, -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-$OC(CH_3)_2C_6H_4C_6H_5$, -NH-Bpoc), as a 9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a 2-trimethylsilylethyloxy amide (-NH-Teoc), as a 2,2,2-trichloroethyloxy amide (-NH-Troc), as an allyloxy amide (-NH-Alloc), or as a 2-(phenylsulphonyl)ethyloxy amide (-NH-Psec).

Other protecting groups for amines, such as cyclic amines and heterocyclic N-H groups, include toluenesulphonyl (tosyl) and methanesulphonyl (mesyl) groups and benzyl groups such as a *para*-methoxybenzyl (PMB) group. A carboxylic acid group may be protected as an ester for example, as: an C_{1-7} alkyl ester (e.g., a methyl ester; a t-butyl ester); a C_{1-7} haloalkyl ester (e.g., a C_{1-7} trihaloalkyl ester); a triC_{1-7} alkylsilyl-C_{1-7}alkyl ester; or a C_{5-20} aryl-C_{1-7} alkyl ester (e.g., a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide. A thiol group may be protected, for example, as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether (-S-CH_2NHC(=O)CH_3).

The 1(H) position of the pyrazole group in the compounds of the formula (I) or its precursors can be protected by a variety of groups, the protecting group being selected according to the nature of the reaction conditions to which the group is exposed. Examples of protecting groups for the pyrazole N-H include tetrahydropyranyl, benzyl and 4-methoxybenzyl groups.

Many of the chemical intermediates described above are novel and such novel intermediates form a further aspect of the invention.

Pharmaceutical Formulations

The invention also provides compounds of the formula (I) as hereinbefore defined in the form of pharmaceutical compositions.

The pharmaceutical compositions can be in any form suitable for oral, parenteral, topical, intranasal, ophthalmic, otic, rectal, intra-vaginal, or transdermal administration. Where the compositions are intended for parenteral administration, they can be formulated for intravenous, intramuscular, intraperitoneal, or subcutaneous administration or for direct delivery into a target organ or tissue by injection, infusion or other means of delivery.

Pharmaceutical dosage forms suitable for oral administration include tablets, capsules, caplets, pills, lozenges, syrups, solutions, powders, granules, elixirs and suspensions, sublingual tablets, wafers or patches and buccal patches.

Pharmaceutical compositions containing compounds of the formula (I) can be formulated in accordance with known techniques, see for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, USA.

Thus, tablet compositions can contain a unit dosage of active compound together with an inert diluent or carrier such as a sugar or sugar alcohol, eg; lactose, sucrose, sorbitol or mannitol; and/or a non-sugar derived diluent such as sodium carbonate, calcium phosphate, calcium carbonate, or a cellulose or derivative thereof such as methyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, and starches such as corn starch. Tablets may also contain such standard ingredients as binding and granulating agents such as polyvinylpyrrolidone, disintegrants (e.g. swellable crosslinked polymers such as crosslinked carboxymethylcellulose), lubricating agents (e.g. stearates), preservatives (e.g. parabens), antioxidants (e.g. BHT), buffering agents (for example phosphate or citrate buffers), and effervescent agents such as citrate/bicarbonate mixtures. Such excipients are well known and do not need to be discussed in detail here.

Capsule formulations may be of the hard gelatin or soft gelatin variety and can contain the active component in solid, semi-solid, or liquid form. Gelatin capsules can be formed from animal gelatin or synthetic or plant derived equivalents thereof.

The solid dosage forms (e.g. tablets, capsules etc.) can be coated or un-coated, but typically have a coating, for example a protective film coating (e.g. a wax or varnish) or a release controlling coating. The coating (e.g. a Eudragit ™ type polymer) can be designed to release the active component at a desired location within the gastro-intestinal tract. Thus, the coating can be selected so as to degrade under certain pH conditions within the gastrointestinal tract, thereby selectively release the compound in the stomach or in the ileum or duodenum.

Instead of, or in addition to, a coating, the drug can be presented in a solid matrix comprising a release controlling agent, for example a release delaying agent which may be adapted to selectively release the compound under conditions of varying acidity or alkalinity in the gastrointestinal tract. Alternatively, the matrix material

or release retarding coating can take the form of an erodible polymer (e.g. a maleic anhydride polymer) which is substantially continuously eroded as the dosage form passes through the gastrointestinal tract.

Compositions for topical use include ointments, creams, sprays, patches, gels, liquid drops and inserts (for example intraocular inserts). Such compositions can be formulated in accordance with known methods.

Compositions for parenteral administration are typically presented as sterile aqueous or oily solutions or fine suspensions, or may be provided in finely divided sterile powder form for making up extemporaneously with sterile water for injection.

Examples of formulations for rectal or intra-vaginal administration include pessaries and suppositories which may be, for example, formed from a shaped mouldable or waxy material containing the active compound.

Compositions for administration by inhalation may take the form of inhalable powder compositions or liquid or powder sprays, and can be administrated in standard form using powder inhaler devices or aerosol dispensing devices. Such devices are well known. For administration by inhalation, the powdered formulations typically comprise the active compound together with an inert solid powdered diluent such as lactose.

The compounds of the inventions will generally be presented in unit dosage form and, as such, will typically contain sufficient compound to provide a desired level of biological activity. For example, a formulation intended for oral administration may contain from 0.1 milligrams to 2 grams of active ingredient, more usually from 10 milligrams to 1 gram, for example, 50 milligrams to 500 milligrams.

The active compound will be administered to a patient in need thereof (for example a human or animal patient) in an amount sufficient to achieve the desired therapeutic effect.

Protein Kinase Inhibitory Activity

The activity of the compounds of the invention as inhibitors of protein kinases A and B can be measured using the assays set forth in the examples below and the level of activity exhibited by a given compound can be defined in terms of the IC50 value. Preferred compounds of the present invention are compounds having an IC_{50} value of less than 1 micromole, more preferably less than 0.1 micromole.

Therapeutic Uses

Prevention or Treatment of Proliferative Disorders

The compounds of the formula (I) are inhibitors of protein kinase A and protein kinase B. As such, they are expected to be useful in providing a means of preventing the growth or inducing apoptosis of neoplasias. It is therefore anticipated that the compounds will prove useful in treating or preventing proliferative disorders such as cancers. In particular tumours with deletions or inactivating mutations in PTEN may be particularly sensitive to PKB inhibitors. Tumours which have other abnormalities leading to an upregulated PKB pathway signal may also be particularly sensitive to inhibitors of PKB. Examples of such abnormalities include but are not limited to overexpression of one or more PI3K subunits, over-expression of one or more PKB isoforms, or mutations in PI3K, PDK1, or PKB which lead to an increase in the basal activity of the enzyme in question.

It is also envisaged that the compounds of the invention will be useful in treating other conditions which result from disorders in proliferation or survival such as viral infections, and neurodegenerative diseases for example. PKB plays an important role in maintaining the survival of immune cells during an immune response and therefore PKB inhibitors could be particularly beneficial in immune disorders including autoimmune conditions.

Therefore, PKB inhibitors could be useful in the treatment of diseases in which there is a disorder of proliferation, apoptosis or differentiation.

Examples of cancers which may be inhibited include, but are not limited to, a carcinoma, for example a carcinoma of the bladder, breast, colon (e.g. colorectal carcinomas such as colon adenocarcinoma and colon adenoma), kidney, epidermal, liver, lung, for example adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas, oesophagus, gall bladder, ovary, pancreas e.g. exocrine pancreatic carcinoma, stomach, cervix, thyroid, prostate, or skin, for example squamous cell carcinoma; a hematopoietic tumour of lymphoid lineage, for example leukaemia, acute lymphocytic leukaemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, or Burkett's lymphoma; a hematopoietic tumour of myeloid lineage, for example acute and chronic myelogenous leukaemias, myelodysplastic syndrome, or promyelocytic leukaemia; thyroid follicular cancer; a tumour of mesenchymal origin, for example fibrosarcoma or habdomyosarcoma; a tumour of the central or peripheral nervous system, for example astrocytoma, neuroblastoma, glioma or schwannoma; melanoma; seminoma; teratocarcinoma; osteosarcoma; xenoderoma pigmentosum; keratoctanthoma; thyroid follicular cancer; or Kaposi's sarcoma.

Thus, in the pharmaceutical compositions, uses or methods of this invention for treating a disease or condition comprising abnormal cell growth, the disease or condition comprising abnormal cell growth in one embodiment is a cancer.

Particular subsets of cancers include breast cancer, ovarian cancer, colon cancer, prostate cancer, oesophageal cancer, squamous cancer and non-small cell lung carcinomas.

It is also possible that some protein kinase B inhibitors can be used in combination with other anticancer agents. For example, it may be beneficial to combine of an inhibitor that induces apoptosis with another agent which acts via a different mechanism to regulate cell growth thus treating two of the characteristic features of cancer development. Examples of such combinations are set out below.

Immune Disorders

Immune disorders for which PKA and PKB inhibitors may be beneficial include but are not limited to autoimmune conditions and chronic inflammatory diseases, for example systemic lupus erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus, Eczema hypersensitivity reactions, asthma, COPD, rhinitis, and upper respiratory tract disease.

Other Therapeutic Uses

PKB plays a role in apoptosis, proliferation, differentiation and therefore PKB inhibitors could also be useful in the treatment of the following diseases other than cancer and those associated with immune dysfunction; viral infections, for example herpes virus, pox virus, Epstein-Barr virus, Sindbis virus, adenovirus, HIV, HPV, HCV and HCMV; prevention of AIDS development in HIV-infected individuals; cardiovascular diseases for example cardiac hypertrophy, restenosis, atherosclerosis; neurodegenerative disorders, for example Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotropic lateral sclerosis, retinitis pigmentosa, spinal muscular atropy and cerebellar degeneration; glomerulonephritis; myelodysplastic syndromes, ischemic injury associated myocardial infarctions, stroke and reperfusion injury, degenerative diseases of the musculoskeletal system, for example, osteoporosis and arthritis, aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases.

Methods of Treatment

It is envisaged that the compounds of the formula (I) will useful in the prophylaxis or treatment of a range of disease states or conditions mediated by protein kinase A and/or protein kinase B. Examples of such disease states and conditions are set out above.

Compounds of the formula (I) are generally administered to a subject in need of such administration, for example a human or animal patient, preferably a human.

The compounds will typically be administered in amounts that are therapeutically or prophylactically useful and which generally are non-toxic. However, in certain situations (for example in the case of life threatening diseases), the benefits of administering a compound of the formula (I) may outweigh the disadvantages of any toxic effects or side effects, in which case it may be considered desirable to administer compounds in amounts that are associated with a degree of toxicity.

The compounds may be administered over a prolonged term to maintain beneficial therapeutic effects or may be administered for a short period only. Alternatively they may be administered in a pulsatile manner.

A typical daily dose of the compound can be in the range from 100 picograms to 100 milligrams per kilogram of body weight, more typically 10 nanograms to 10 milligrams per kilogram of bodyweight although higher or lower doses may be administered where required. Ultimately, the quantity of compound administered will be commensurate with the nature of the disease or physiological condition being treated and will be at the discretion of the physician.

The compounds of the formula (I) can be administered as the sole therapeutic agent or they can be administered in combination therapy with one of more other compounds for treatment of a particular disease state, for example a neoplastic disease such as a cancer as hereinbefore defined. Examples of other therapeutic agents that may be administered together (whether concurrently or at different time intervals) with the compounds of the formula (I) include but are not limited to topoisomerase inhibitors, alkylating agents, antimetabolites, DNA binders and microtubule inhibitors, such as cisplatin, cyclophosphamide, doxorubicin, irinotecan, fludarabine, 5FU, taxanes, mitomycin C or radiotherapy. For the case of protein kinase B inhibitors combined with other therapies the two or more treatments may be given in individually varying dose schedules and via different routes.

Where the compound of the formula (I) is administered in combination therapy with one or more other therapeutic agents, the compounds can be administered simultaneously or sequentially. When administered sequentially, they can be

administered at closely spaced intervals (for example over a period of 5-10 minutes) or at longer intervals (for example 1, 2, 3, 4 or more hours apart, or even longer periods apart where required), the precise dosage regimen being commensurate with the properties of the therapeutic agent(s).

The compounds of the invention may also be administered in conjunction with non-chemotherapeutic treatments such as radiotherapy, photodynamic therapy, gene therapy; surgery and controlled diets.

For use in combination therapy with another chemotherapeutic agent, the compound of the formula (I) and one or more other therapeutic agents can be, for example, formulated together in a dosage form containing two or more therapeutic agents. In an alternative, the individual therapeutic agents may be formulated separately and presented together in the form of a kit, optionally with instructions for their use.

EXPERIMENTAL

The invention will now be illustrated, but not limited, by reference to the specific embodiments described in the following procedures and examples.

The starting materials for each of the procedures described below are commercially available unless otherwise specified.

In the examples, the compounds prepared were characterised by liquid chromatography, mass spectroscopy and ^{1}H nuclear magnetic resonance spectroscopy using the systems and operating conditions set out below.

Proton magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AV400 instrument operating at 400.13MHz, in Me-d_3-OD at 27C, unless otherwise stated and are reported as follows: chemical shift δ/ppm (number of protons, multiplicity where s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad). The residual protic solvent MeOH (δ_H = 3.31 ppm) was used as the internal reference.

For the mass spectra, where chlorine is present, the mass quoted for the compound is for ^{35}Cl.

A number of liquid chromatography systems were used and these are described below.

Platform System

HPLC System: Waters 2795

Mass Spec Detector: Micromass Platform LC

PDA Detector: Waters 2996 PDA

Acidic Analytical conditions 1:

Eluent A: H_2O (0.1% Formic Acid)

Eluent B: CH_3CN (0.1% Formic Acid)

Gradient: 5-95% eluent B over 3.5 minutes

Flow: 1.5 ml/min

Column: Phenomenex Synergi 4µ Max-RP 80A, 50x4.6mm

Acidic Analytical conditions 2:

Eluent A: H_2O (0.1% Formic Acid)

Eluent B: CH_3CN (0.1% Formic Acid)

Gradient: 5-95% eluent B over 3.5 minutes

Flow: 0.8 ml/min

Column: Phenomenex Synergi 4µ Max-RP 80A, 50x2.0mm

Acidic Analytical conditions 3:

Eluent A: H_2O (0.1% Formic Acid)

Eluent B: CH_3CN (0.1% Formic Acid)

Gradient: 5-95% eluent B over 15 minutes

Flow: 0.4 ml/min

Column: Phenomenex Synergi 4µ Max-RP 80A, 50x2.0mm

Basic Analytical conditions 1:

Eluent A: H_2O (10mM NH_4HCO_3 buffer adjusted to pH=9.5 with NH_4OH)

Eluent B: CH_3CN

Gradient: 05-95% eluent B over 3.5 minutes

Flow: 1.5 ml/min

Column: Waters XTerra MS C_{18} 5µm 4.6x50mm

Basic Analytical conditions 2:

Eluent A: H_2O (10mM NH_4HCO_3 buffer adjusted to pH=9.5 with NH_4OH)

Eluent B: CH_3CN

Gradient: 05-95% eluent B over 3.5 minutes

Flow: 0.8 ml/min

Column: Thermo Hypersil-Keystone BetaBasic-18 5µm, 50x2.1mm

Basic Analytical conditions 3:

Eluent A: H_2O (10mM NH_4HCO_3 buffer adjusted to pH=9.5 with NH_4OH)

Eluent B: CH_3CN

Gradient: 05-95% eluent B over 3.5 minutes

Flow: 0.8 ml/min

Column: Phenomenex Luna C18(2) 5µm, 50x2.0mm

Polar Analytical conditions:

Eluent A: H_2O (0.1% Formic Acid)

Eluent B: CH_3CN (0.1% Formic Acid)

Gradient: 00-50% eluent B over 3 minutes

Flow: 1.5 ml/min

Column: Phenomenex Synergi 4µ Hydro 80A, 50x4.6mm

MS conditions:

Capillary voltage: 3.5 kV or 3.6 kV

Cone voltage: 30 V

Source Temperature: 120 °C

Scan Range: 165-700 amu

Ionisation Mode: ElectroSpray Negative, Positive or Positive & Negative

FractionLynx System

System:	Waters FractionLynx (dual analytical/prep)
HPLC Pump:	Waters 2525
Injector-Autosampler:	Waters 2767
Mass Spec Detector:	Waters-Micromass ZQ
PDA Detector:	Waters 2996 PDA

Acidic Analytical conditions:

Eluent A:	H_2O (0.1% Formic Acid)
Eluent B:	CH_3CN (0.1% Formic Acid)
Gradient:	5-95% eluent B over 5 minutes
Flow:	2.0 ml/min
Column:	Phenomenex Synergi 4µ Max-RP 80A, 50x4.6mm

Polar Analytical conditions:

Eluent A:	H_2O (0.1% Formic Acid)
Eluent B:	CH_3CN (0.1% Formic Acid)
Gradient:	00-50% eluent B over 5 minutes
Flow:	2.0 ml/min
Column:	Phenomenex Synergi 4µ Max-RP 80A, 50x4.6mm

MS parameters for acidic and polar analytical conditions:

Capillary voltage:	3.5 kV
Cone voltage:	25 V
Source Temperature:	120 °C
Scan Range:	125-800 amu
Ionisation Mode:	ElectroSpray Positive or ElectroSpray Positive & Negative

Chiral Analytical conditions:

Eluent:	MeOH + 0.1% NH4/TFA
Flow:	1.2 ml/min
Total time:	16.00min
Inj. Volume:	10µL

Sample conc.: 2mg/ml

Column: Astec, Chirobiotic V; 250x4.6 mm

Mass spectrometer was taken off-line.

Agilent System

HPLC System: Agilent 1100 series

Mass Spec Detector: Agilent LC/MSD VL

Multi Wavelength Detector: Agilent1100 series MWD

Software: HP Chemstation

Chiral Analytical conditions:

Eluent: MeOH + 0.2% NH4/AcOH at room Temperature

Flow: 2.0 ml/min

Total time: 8.5 min

Inj. Volume: 20 uL

Sample Conc: 2 mg/ml

Column: Astec, Chirobiotic V; 250x4.6 mm

Chiral Preparative conditions 1:

Eluent: MeOH + 0.1% NH4/TFA at room Temperature

Flow: 6.0 ml/min

Total time: 10 min

Inj. Volume: 100 uL

Sample Conc: 20 mg/ml

Column: Astec, Chirobiotic V; 250x10 mm

Chiral Preparative conditions 2:

Eluent: MeOH + 0.2% NH4/AcOH at room Temperature

Flow: 20.0 ml/min

Total time: 19 min

Inj. Volume: 950 uL

Sample Conc: 25 mg/ml

Column: Astec, Chirobiotic V2; 250x21.2 mm

MS conditions (just analytical method):

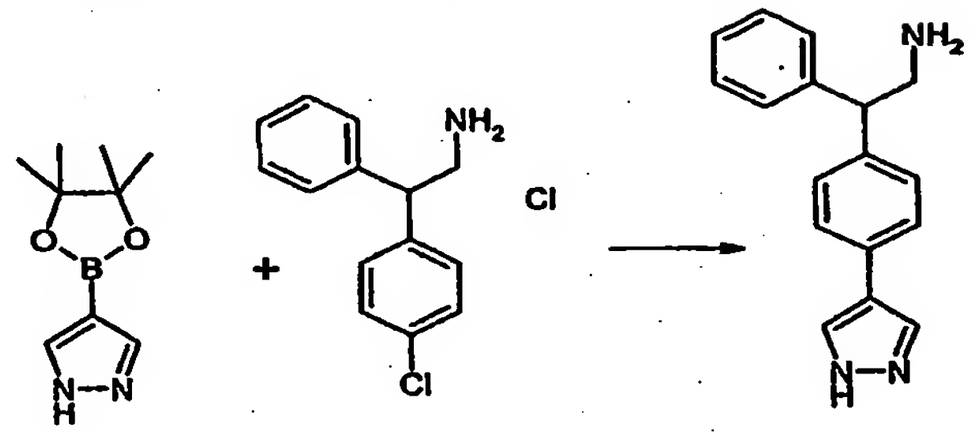
Capillary voltage:	3000 V
Fragmentor:	150
Gain:	1.00
Drying gas:	12.0 L/min
Drying gas T:	350 °C
Nebulizer pressure:	35 (psig)
Scan Range:	125-800 amu
Ionisation Mode:	ElectroSpray Positive

In the examples below, the following key is used to identify the LCMS conditions used:

PS-A	Platform System – acidic analytical conditions 1
PS-A2	Platform System – acidic analytical conditions 2
PS-A3	Platform System – acidic analytical conditions 3
PS-B	Platform System –basic analytical conditions 1
PS-B2	Platform System –basic analytical conditions 2
PS-B3	Platform System –basic analytical conditions 3
PS-P	Platform System – polar analytical conditions
FL-A	FractionLynx System – acidic analytical conditions
FL-P	FractionLynx System – polar analytical conditions
FL-C	FractionLynx System – chiral analytical conditions
AG-CA	Agilent System – chiral analytical conditions
AG-CP1	Agilent System – chiral preparative conditions 1
AG-CP2	Agilent System – chiral preparative conditions 2

EXAMPLE 1

2-Phenyl-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethylamine

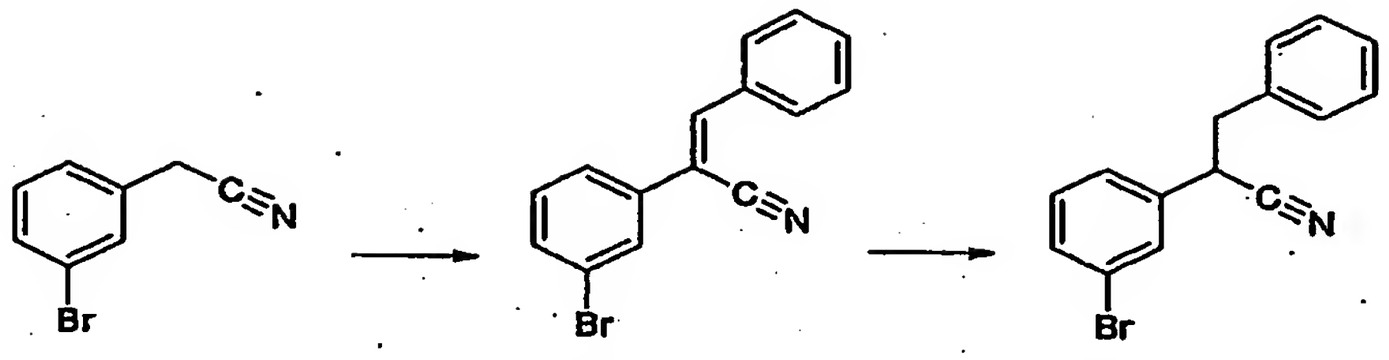


To a suspension of 2-(4-chlorophenyl)-2-phenylethylamine hydrochloride (134 mg, 0.5 mmol, 1.0 equiv.) (Array PPA-Q02-1) in toluene (0.8 ml) was added bis(tri-t-butylphosphine)palladium (0) (3 mg, 1 mol%) (Strem) and the mixture was purged with nitrogen. A suspension of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (107 mg, 0.55 mmol, 1.1 equiv.) (Aldrich 52,505-7) in ethanol (0.8 ml) was added followed by potassium carbonate (415 mg, 3.0 mmol, 6 equiv.) in water (2.5 ml). The mixture was purged with nitrogen and sealed. The reaction mixture was heated in a CEM Explorer™ microwave to 135 °C for 15 minutes using 50 watts power. The solvents were removed and the residue was partitioned between ethyl acetate and 2N NaOH. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (SiO_2), eluting with a mixture of dichloromethane (90ml): methanol (18ml): acetic acid (3ml): H_20 (2ml) to afford the title compound 14 mg (9%); LCMS (PS-A) R_t 1.79 min; *m/z* $[M+H]^+$ 264.

EXAMPLE 2

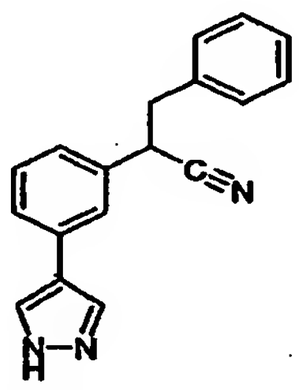
3-Phenyl-2-[3-(1H-pyrazol-4-yl)-phenyl]-propionitrile

2A. 2-(3-Bromo-phenyl)-3-phenyl-propionitrile



A solution of 40% KOH (2.83 g in 5.0 ml of H_2O) in ethanol (13 ml) was added to a solution of benzaldehyde (2.85 ml, 28.05 mmol) and 3-bromophenylacetonitrile (5 g, 25.50 mmol) in ethanol (9 ml). The reaction mixture was then stirred at room temperature for 2 hours and the precipitate was collected by suction filtration and washed with cold ethanol (6.68 g, 92 %). The crude product (3.45g, 12.14 mmol) was then dissolved in ethanol (35 ml) and heated to 65 °C. Sodium borohydride (459 mg, 12.14 mmol) was added in portions and the reaction mixture was maintained at this temperature for a further 2 hours. Upon cooling, water (10 ml) was added and the solvent was removed under reduced pressure. The residue was partitioned between water (100 ml) and ethyl acetate (100 ml). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated to afford the desired product (1.80 g, 52 %), which was used without purification.

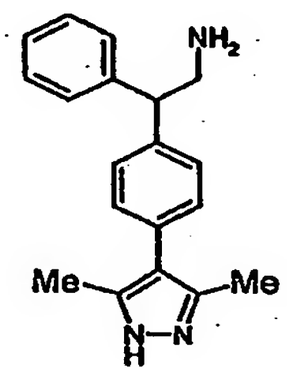
2B. 3-Phenyl-2-[3-(1H-pyrazol-4-yl)-phenyl]-propionitrile



2-(3-Bromo-phenyl)-3-phenyl-propionitrile was reacted with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole following the procedure set out in Example 1 to give the title compound. (LC/MS: (PS-A) R_t 2.98 $[M+H]^+$ 274).

EXAMPLE 3

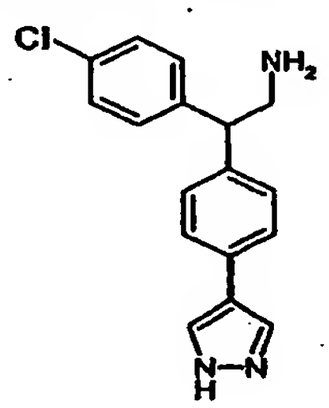
2-[4-(3,5-Dimethyl-1H-pyrazol-4-yl)-phenyl]-2-phenyl-ethylamine



Following the procedure of Example 1 but using 3,5-dimethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (Boron Molecular D03-BM152) instead of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole gave the title compound. (LC/MS: (PS-A) R_t 1.79 $[M+H]^+$ 292.

EXAMPLE 4

2-(4-Chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethylamine



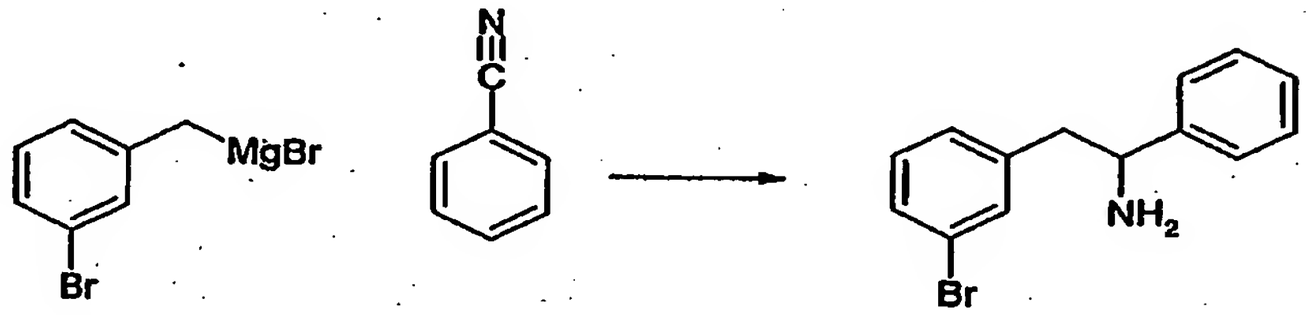
Following the procedure of Example 1 but using 2,2-bis-(4-chloro-phenyl)-ethylamine in place of 2-(4-chlorophenyl)-2-phenylethylamine hydrochloride* gave the title compound. (LC/MS: (PS-A) R_t 1.99 $[M+H]^+$ 298).

*This starting material can be made by the method described in *J. Amer. Chem. Soc.*, 1983, 105, 3183-3188.

EXAMPLE 5

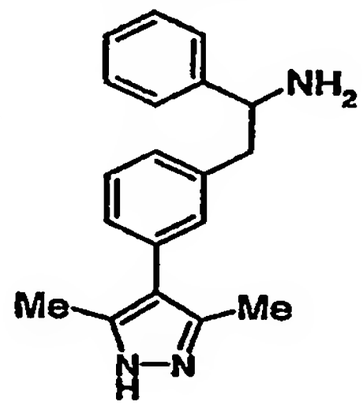
2-[3-(3,5-Dimethyl-1H-pyrazol-4-yl)-phenyl]-1-phenyl-ethylamine

5A. 2-(3-Bromo-phenyl)-1-phenyl-ethylamine



Benzonitrile (500 mg, 4.849 mmol) was added dropwise to a solution of 3-bromobenzylmagnesium bromide (0.275 M solution in diethyl ether, 21.1 ml, 5.818 mmol) under an atmosphere of nitrogen at room temperature. The reaction mixture was then heated to reflux for a period of 2 hours then allowed to cool. Lithium aluminium hydride (1.0 M in THF, 4.85 ml, 4.849 mmol) was then added cautiously and the reaction mixture was allowed to heat at reflux for a further 16 hours. Upon cooling, the reaction was quenched by cautious and dropwise addition of water (5 ml) and then partitioned between water (20 ml) and ethyl acetate (100 ml). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated. Purification by ion exchange chromatography afforded the desired compound (420 mg, 31 %).

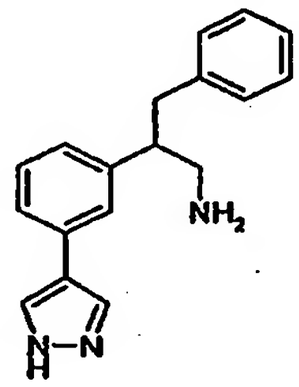
5B. 2-[3-(3,5-Dimethyl-1H-pyrazol-4-yl)-phenyl]-1-phenyl-ethylamine



The product of 5B was reacted with 3,5-dimethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole following the procedure set out in Example 1 to give the title compound. (LC/MS: (PS-B) R_t 2.54 $[M+H]^+$ 292).

EXAMPLE 6

3-Phenyl-2-[3-(1H-pyrazol-4-yl)-phenyl]-propylamine

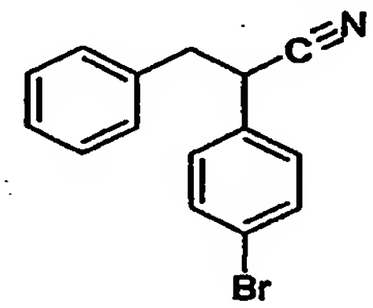


To a solution of the product of Example 2 (70 mg, 0.256 mmol, 1.0 equiv) in ethanol (25 ml) was added concentrated ammonia (0.5 ml) and Raney Nickel (approximately 0.5 ml of the water suspension) and the reaction mixture was subjected to a hydrogen atmosphere for 17 hours. The mixture was filtered through Celite® and the mother liquor was concentrated under reduced pressure to give the title compound which was purified by preparative liquid chromatography. (LC/MS: (PS-A) R_t 1.89 $[M+H]^+$ 278.

EXAMPLE 7

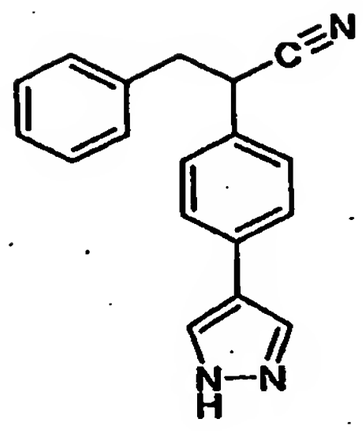
3-Phenyl-2-[4-(1H-pyrazol-4-yl)-phenyl]-propylamine

7A. 2-(4-Bromo-phenyl)-3-phenyl-propionitrile



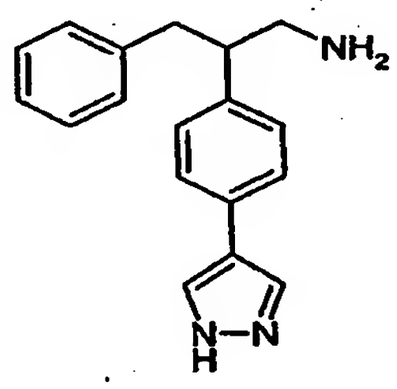
Following the procedure described in Example 2A but substituting 4-bromophenylacetonitrile for 3-bromophenylacetonitrile gave the title compound was obtained which was used in the next step without further purification.

7B. 3-Phenyl-2-[4-(1H-pyrazol-4-yl)-phenyl]-propionitrile



By following the procedure described in Example 1 but substituting 2-(4-Bromo-phenyl)-3-phenyl-propionitrile for 2-(4-chlorophenyl)-2-phenylethylamine, the title compound was obtained.

7C. 3-Phenyl-2-[4-(1H-pyrazol-4-yl)-phenyl]-propylamine



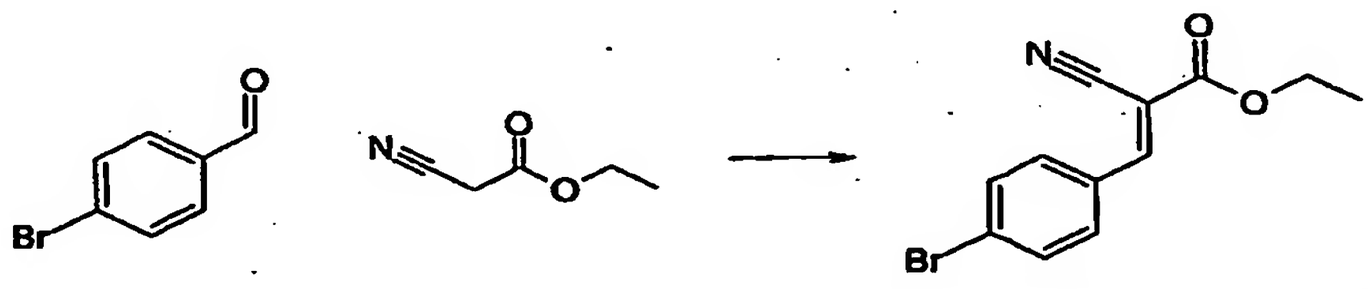
The nitrile product of Example 7B was reduced using the conditions described in Example 6 to give the title compound. (LC/MS: (PS-B) R_t 3.03 $[M+H]^+$ 278.

EXAMPLE 8

{3-(4-Chloro-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-methyl-amine

8A. 3-(4-Bromo-phenyl)-2-cyano-acrylic acid ethyl ester

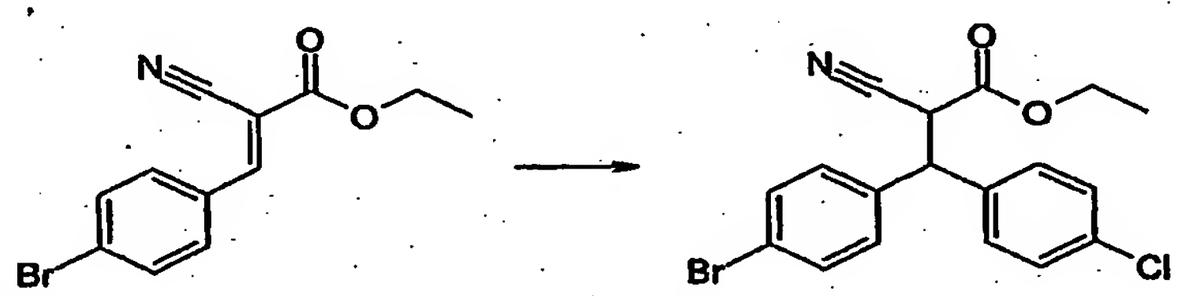
(J.Med.Chem, 1983, 26, 935-947)



4-Bromobenzaldehyde (3g, 16.21 mmol) and ethyl cyanoacetate (1.9 ml, 17.84 mmol) in toluene was added piperidine (27 µl) and the reaction mixture was refluxed for 1 hour with a Dean-Stark separator. The solvent was removed under

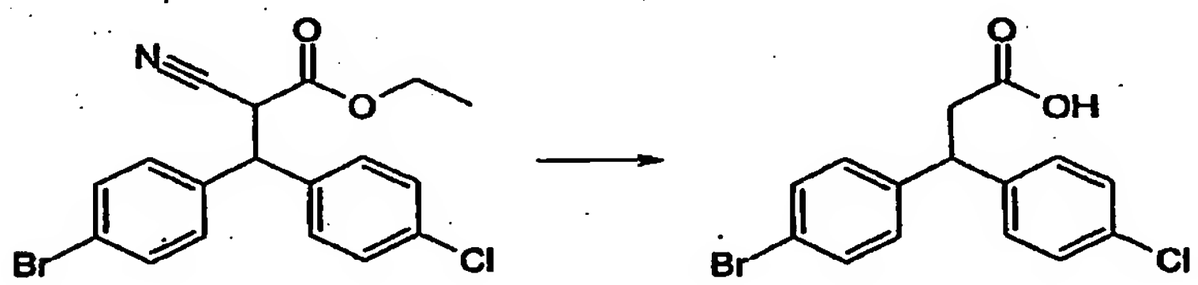
reduced pressure, the residue triturated with warm ethyl acetate, filtered to yield the desired product as a yellow solid (4.03g, 89% yield). LC/MS: (PS-A2) R_t 3.44.

8B. 3-(4-Bromo-phenyl)-3-(4-chloro-phenyl)-2-cyano-propionic acid ethyl ester



A solution of 3-(4-bromo-phenyl)-2-cyano-acrylic acid ethyl ester (1.5g, 5.36mmol) in dry toluene (12ml) was added dropwise to 4-chlorophenylmagnesium bromide (0.5 M solution in tetrahydrofuran, 6.96 ml, 6.96 mmol) at 0 °C. The reaction mixture was heated to 85 °C for 3 hours, poured onto ice, acidified with 1N HCl and extracted with ethyl acetate. The organic layer was separated, dried ($MgSO_4$), filtered and concentrated, the crude product was purified over flash silica chromatography eluting with petroleum ether to ethyl acetate/petroleum ether (5:95) to afford the desired product (1.91g, 91% yield). LC/MS: (PS-A2) R_t 3.78 $[M+H]^+$ 391.93.

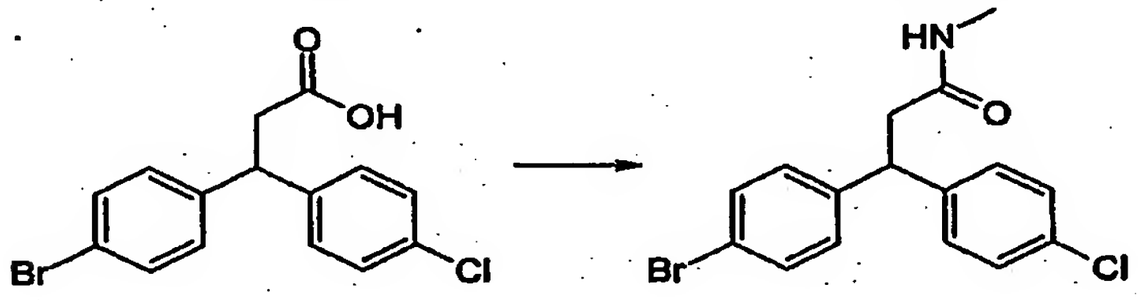
8C. 3-(4-Bromo-phenyl)-3-(4-chloro-phenyl)-propionic acid



A mixture of 3-(4-bromo-phenyl)-3-(4-chloro-phenyl)-2-cyano-propionic acid ethyl ester (1.91, 4.87 mmol), acetic acid (10 ml), concentrated sulfuric acid (5 ml) and water (5 ml) were refluxed for 2 hours. Reaction mixture was poured into iced water and extracted with ethyl acetate. The organic layer was separated, dried ($MgSO_4$), filtered and concentrated, the crude product was purified over flash silica chromatography eluting with ethyl acetate/petroleum ether (1:1) to

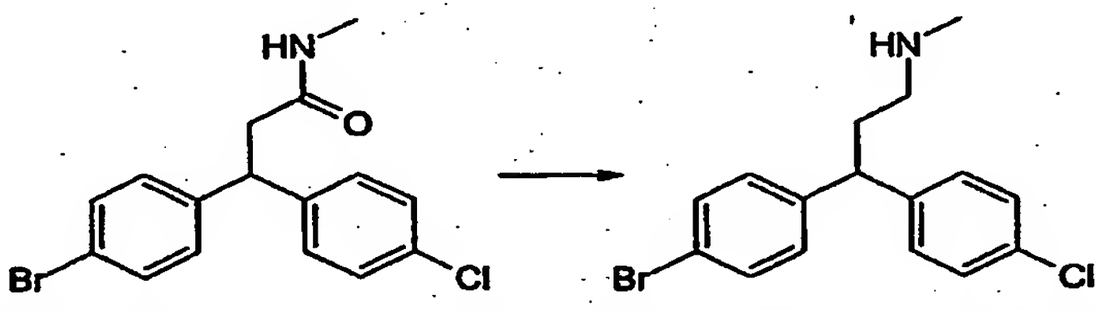
afford the desired product (0.82g, 50% yield). LC/MS: (PS-A2) R_t 3.39 $[M+H]^+$ 338.86.

8D. 3-(4-Bromo-phenyl)-3-(4-chloro-phenyl)-N-methyl-propionamide



A mixture of 3-(4-bromo-phenyl)-3-(4-chloro-phenyl)-propionic acid (0.25g, 0.74mmol) and 1-hydroxybenatriazole (0.12g, 0.88mmol) in dichloromethane (3ml) was stirred for 15 minutes before addition of methylamine (40% solution in water, 0.11µl, 1.47mmol) and 1-(3-dimethylaminopropyl)-ethylcarbodiimide hydrochloride (0.17g, 0.88mmol). The reaction mixture was stirred for 16 hours, solvent removed under reduced pressure and the residue partitioned between ethyl acetate and 1N HCl. The organic layer was separated, washed with saturated sodium hydrogen carbonate, brine, dried ($MgSO_4$), filtered and concentrated to yield the title compound which was used in the next step without further purification. LC/MS: (PS-A2) R_t 3.20 $[M+H]^+$ 353.95.

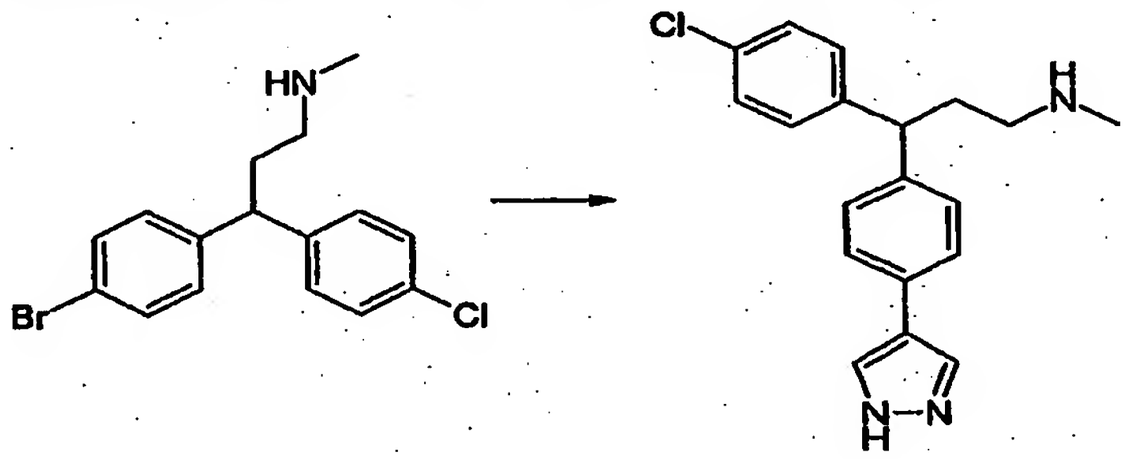
8E. [3-(4-Bromo-phenyl)-3-(4-chloro-phenyl)-propyl]-methyl-amine



Under a nitrogen atmosphere, the crude 3-(4-bromo-phenyl)-3-(4-chloro-phenyl)-N-methyl-propionamide was cooled to 0 °C, lithium aluminum hydride (0.075g, 1.97mmol) and diethyl ether (3ml) were added. With cooling, aluminum chloride (0.23g, 1.69mmol) was dissolved in diethyl ether (2ml) and added. The reaction mixture was stirred for 16 hours, quenched with addition of water, basified (2N NaOH) and extracted with ethyl acetate. The organic layer was separated, dried ($MgSO_4$), filtered and concentrated, the crude product was purified over Phenomenex_Strata_SCX column chromatography eluting with methanol

followed by 2N ammonia in methanol to afford the desired product (0.254g, 62% yield for steps 1D and 1E combined). LC/MS: (PS-B3) R_t 3.20 $[M+H]^+$ 339.85.

8F. {3-(4-Chloro-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-methyl-amine

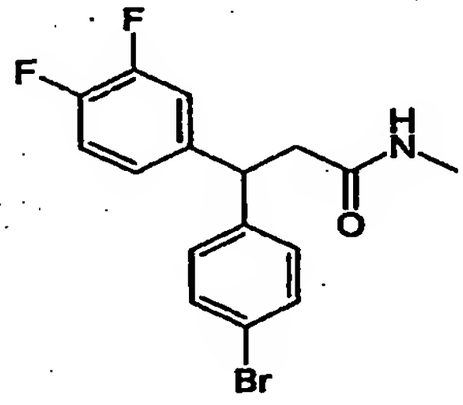


[3-(4-Bromo-phenyl)-3-(4-chloro-phenyl)-propyl]-methyl-amine was reacted with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole following the procedure set out in Example 1 to give the title compound. LC/MS: (PS-B3) R_t 2.63 $[M+H]^+$ 326.00. ^{1}H NMR (Me-d_3-OD) δ 2.37-2.47 (2H, m), 2.66 (3H, s), 2.91 (2H, t), 4.05 (1H, t), 7.25-7.34 (6H, m), 7.54 (2H, d), 7.92 (2H, s), 8.51 (1H, br s).

EXAMPLE 9

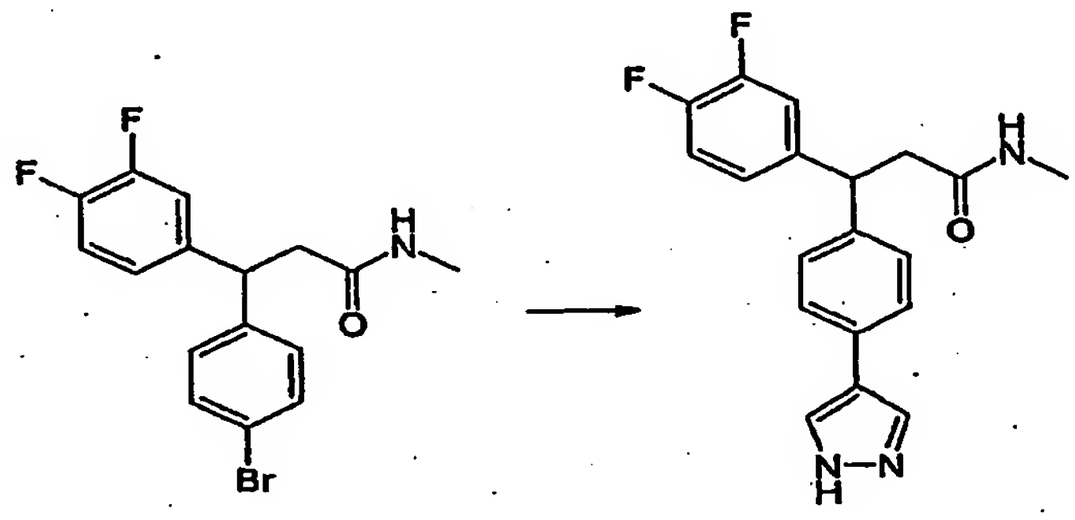
{3-(3,4-Difluoro-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-methyl-amine

9A. 3-(4-Bromo-phenyl)-3-(3,4-difluoro-phenyl)-N-methyl-propionamide



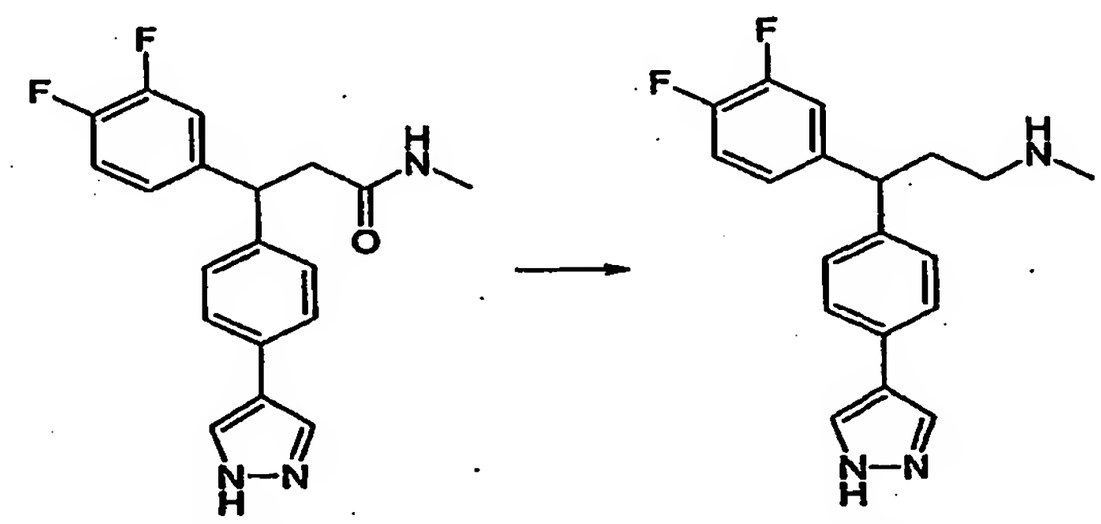
By following the procedure described in Example 8A through to Example 8C but substituting 4-chlorophenylmagnesium bromide for 3,4-difluorophenylmagnesium bromide, the title compound was obtained. LC/MS: (PS-A2) R_t 3.12 $[M+H]^+$ 355.84.

9B.3-(3,4-Difluoro-phenyl)-N-methyl-3-[4-(1H-pyrazol-4-yl)-phenyl]-propionamide



3-(4-Bromo-phenyl)-3-(3,4-difluoro-phenyl)-N-methyl-propionamide was reacted with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole following the procedure set out in Example 1 to give the title compound. LC/MS: (PS-A2) R_t 2.55 $[M+H]^+$ 341.93.

9C. {3-(3,4-Difluoro-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-methyl-amine

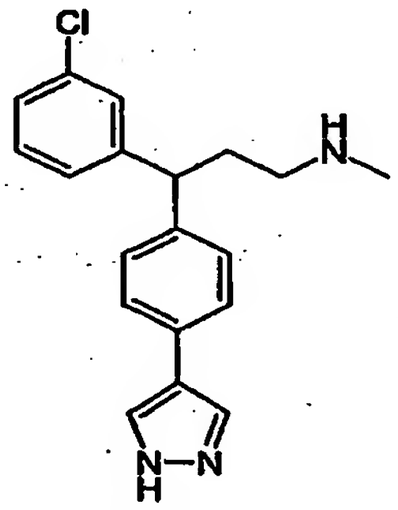


Lithium aluminium hydride was added to a suspension of 3-(3,4-Difluoro-phenyl)-N-methyl-3-[4-(1H-pyrazol-4-yl)-phenyl]-propionamide in diethyl ether, followed by a solution of aluminium chloride in diethyl ether at 0°C, under a nitrogen atmosphere. Toluene was added and the reaction mixture was heated at 70°C for 18 hours. Upon cooling the reaction was quenched with addition of water, basified (2N NaOH) and extracted with ethyl acetate. The organic layer was separated, dried ($MgSO_4$), filtered and concentrated to afford the desired

compound. LC/MS: (PS-A2) R_t 2.15 $[M+H]^+$ 328.06. ^1H NMR (Me-d_3-OD) δ 2.19-2.29 (2H, m), 2.35 (3H, s), 2.51 (2H, t), 4.00 (1H, t), 7.06-7.24 (3H, m), 7.27 (2H, d), 7.52 (2H, d), 7.92 (2H, s).

EXAMPLE 10

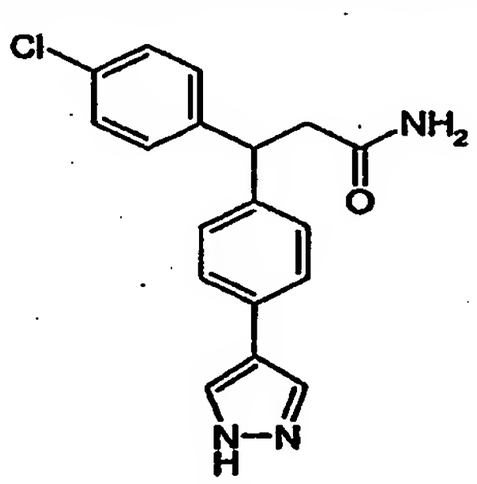
{3-(3-Chloro-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propyl}-methyl-amine



By following the procedure described in Example 8 but substituting 4-chlorophenylmagnesium bromide for 3-chlorophenylmagnesium bromide, the title compound was obtained. LC/MS: (PS-B3) R_t 2.67 $[M+H]^+$ 326.00. ^1H NMR (Me-d_3-OD) δ 2.43-2.50 (2H, m), 2.68 (3H, s), 2.94 (2H, m), 4.13 (1H, t), 7.24 (1H, m), 7.27-7.36 (3H, m), 7.41 (2H, d), 7.66 (2H, d), 8.50 (2H, s).

Example 11

3-(4-Chloro-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propionamide



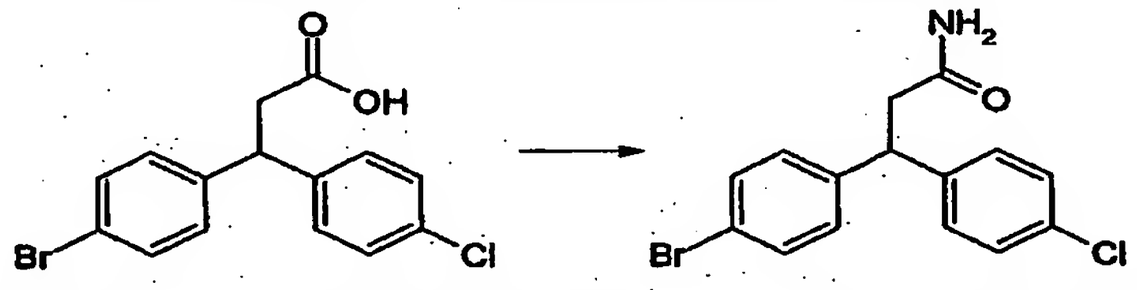
By following the procedure described in Example 9A and 9B but substituting 3,4-difluorophenylmagnesium bromide for 4-chlorophenylmagnesium bromide, the

title compound was obtained. LC/MS: (PS-A2) R_t 2.54 $[M+H]^+$ 326. ^1H NMR (Me-d_3-OD) δ 2.95 (2H, d), 4.53 (1H, t), 7.27 (6H, m), 7.50 (2H, d), 7.91 (2H, s).

EXAMPLE 12

3-(4-Chloro-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propylamine

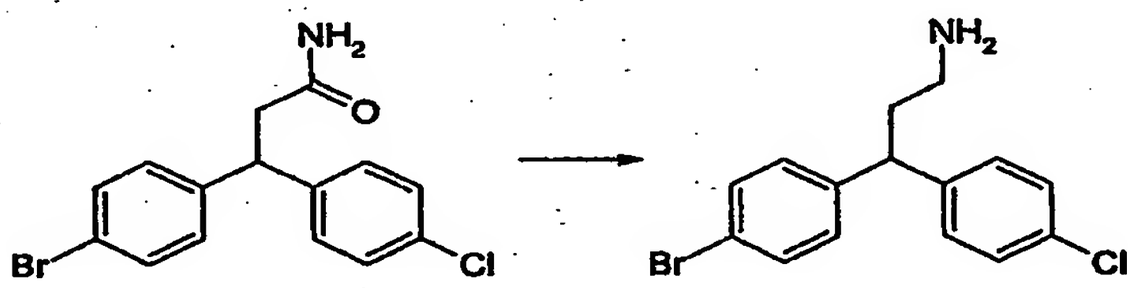
12A. 3-(4-Bromo-phenyl)-3-(4-chloro-phenyl)-propionamide



A solution of 3-(4-Bromo-phenyl)-3-(4-chloro-phenyl)-propionic acid* (0.25g, 0.74mmol) and 1,1'-carbonyldiimidazole (0.24g, 1.47mmol) in dichloromethane was stirred for 45 minutes before the addition of ammonia (2M solution in methanol, 3.68ml, 7.36mmol). The reaction mixture was stirred for 2 hours, solvent removed under reduced pressure and residue was purified over flash silica chromatography eluting with ethyl acetate/petroleum ether (1:4) to afford the title compound (0.091g, 36% yield). LC/MS: (PS-A2) R_t 3.08 $[M+H]^+$ 339.93.

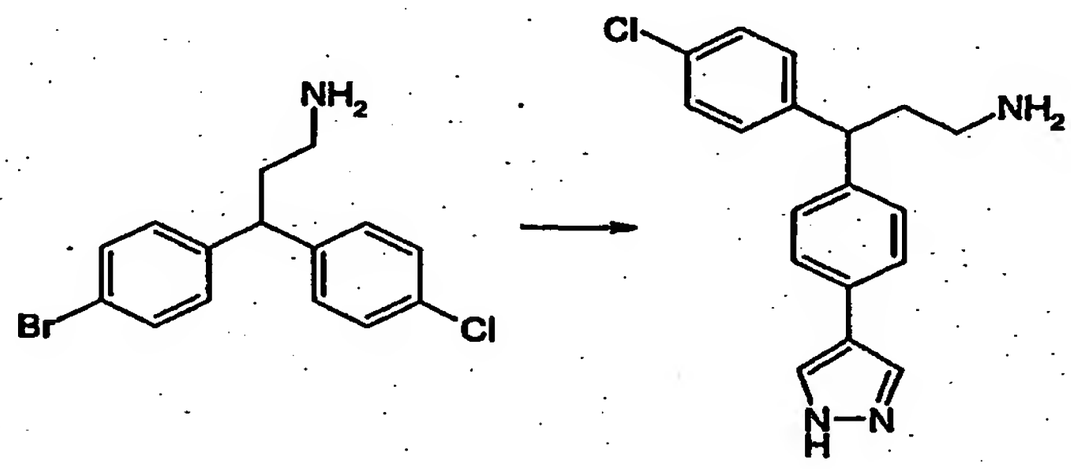
*This starting material can be made by the method described in Example 8A through to 8C.

12B. 3-(4-Bromo-phenyl)-3-(4-chloro-phenyl)-propylamine



By following the procedure described in Example 8E but substituting 3-(4-Bromo-phenyl)-3-(4-chloro-phenyl)-propionamide for 3-(4-Bromo-phenyl)-3-(4-chloro-phenyl)-N-methyl-propionamide, the title compound was obtained. LC/MS: (PS-B2) R_t 3.88 $[M+H]^+$ 359.87.

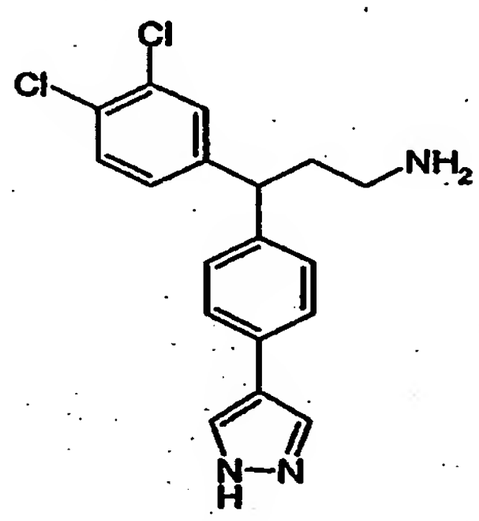
12C. 3-(4-Chloro-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propylamine



3-(4-Bromo-phenyl)-3-(4-chloro-phenyl)-propylamine was reacted with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole following the procedure set out in Example 1 to give the title compound. LC/MS: (PS-B3) R_t 2.54 $[M+H]^+$ 312.04. ^{1}H NMR (Me-d_3-OD) δ 2.39 (2H. m), 2.84 (2H, t), 4.06 (1H, t), 7.27-7.33 (6H, m), 7.54 (2H, d), 7.91 (2H, s).

Example 13

3-(3,4-Dichloro-phenyl)-3-[4-(1H-pyrazol-4-yl)-phenyl]-propylamine

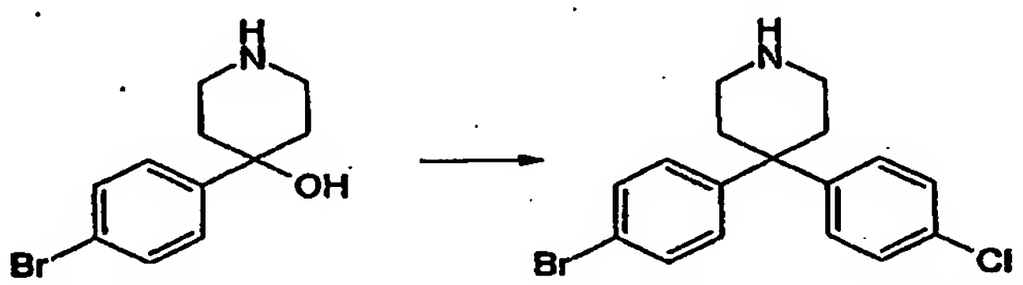


By following the procedure described in Example 12 but substituting 4-chlorophenylmagnesium bromide for 3,4-dichlorophenylmagnesium bromide, the title compound was obtained. LC/MS: (PS-A2) R_t 2.17 $[M+H]^+$ 345.95. ^{1}H NMR (Me-d_3-OD) δ 2.39 (2H, m), 2.84 (2H, t), 4.07 (1H, t), 7.24-7.31 (4H, m), 7.45-7.49 (2H, m), 7.56 (2H, d), 7.93 (2H, s).

EXAMPLE 14

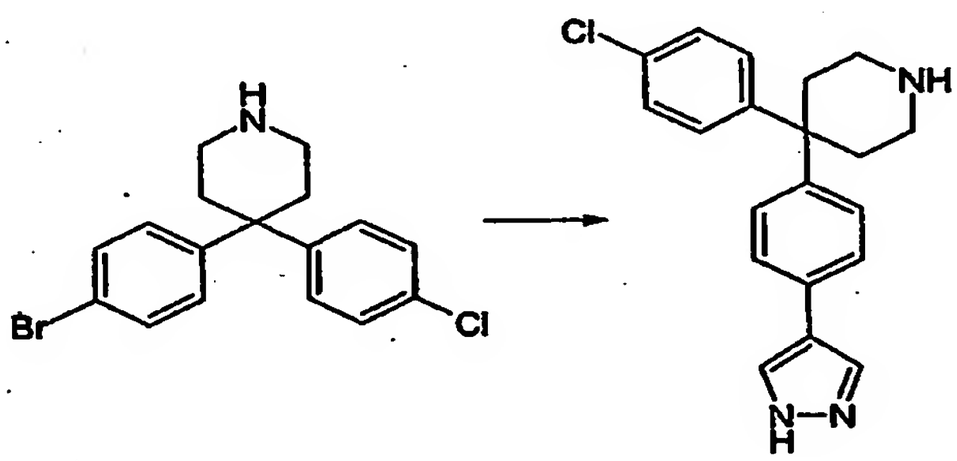
4-(4-Chloro-phenyl)-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine

14A. 4-(4-Bromo-phenyl)-4-(4-chloro-phenyl)-piperidine



A suspension of 4-(4-Bromo-phenyl)-piperidin-4-ol (4.02g, 15.7mmol) in chlorobenzene (30ml) was added dropwise to a suspension of aluminium chloride (7.32g, 54.9mmol) in chlorobenzene (10ml) at 0°C. The reaction mixture was stirred at 0°C for 2 hours, quenched by addition of ice then methyl t-butyl ether added. After stirring for 1 hour the precipitate was collected by filtration washed with water, methyl t-butyl ether and water to afford the title compound (5.59g, 92% yield). LC/MS: (PS-B3) R_t 3.57 $[M+H]^+$ 350, 352.

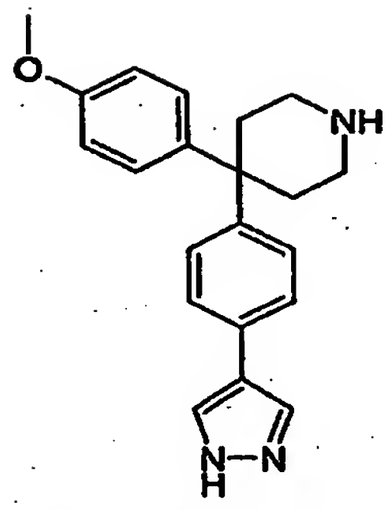
14B. 4-(4-Chloro-phenyl)-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine



4-(4-Bromo-phenyl)-4-(4-chloro-phenyl)-piperidine was reacted with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole following the procedure set out in Example 1 to give the title compound. LC/MS: (PS-A3) R_t 7.22 $[M+H]^+$ 338.08. ^{1}H NMR (Me-d_3-OD) δ 2.64-2.74 (4H, m), 3.22-3.25 (4H, m), 7.33-7.45 (6H, m), 7.65 (2H, d), 8.37 (2H, s).

EXAMPLE 15

4-(4-Methoxy-phenyl)-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine

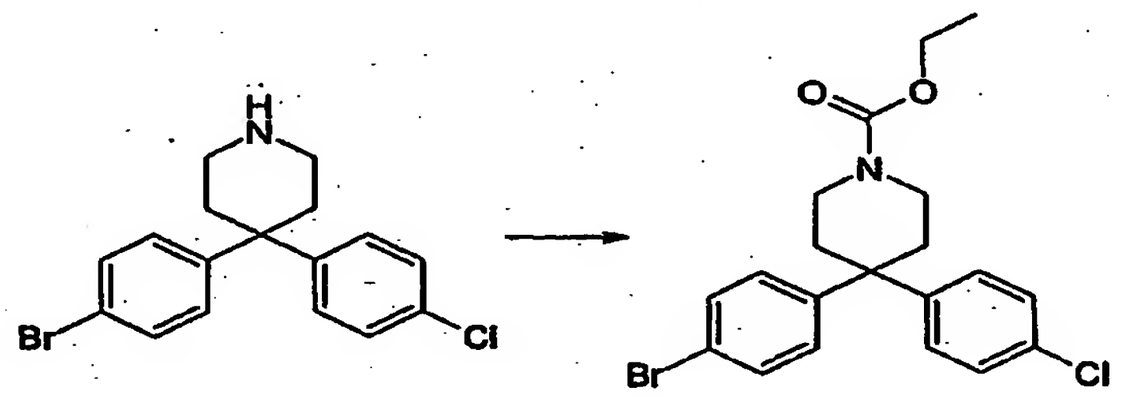


By following the procedure described in Example 14 but substituting chlorobenzene for anisole, the title compound was obtained. LC/MS: (PS-B3) R_t 2.42 $[M+H]^+$ 334.00. ^1H NMR (Me-d_3-OD) δ 2.69 (4H, m), 3.23 (4H, m), 3.76 (3H, s), 6.90 (2H, d), 7.28 (2H, d), 7.40 (2H, d), 7.65 (2H, d), 8.53 (2H, s).

EXAMPLE 16

4-(4-Chloro-phenyl)-1-methyl-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine

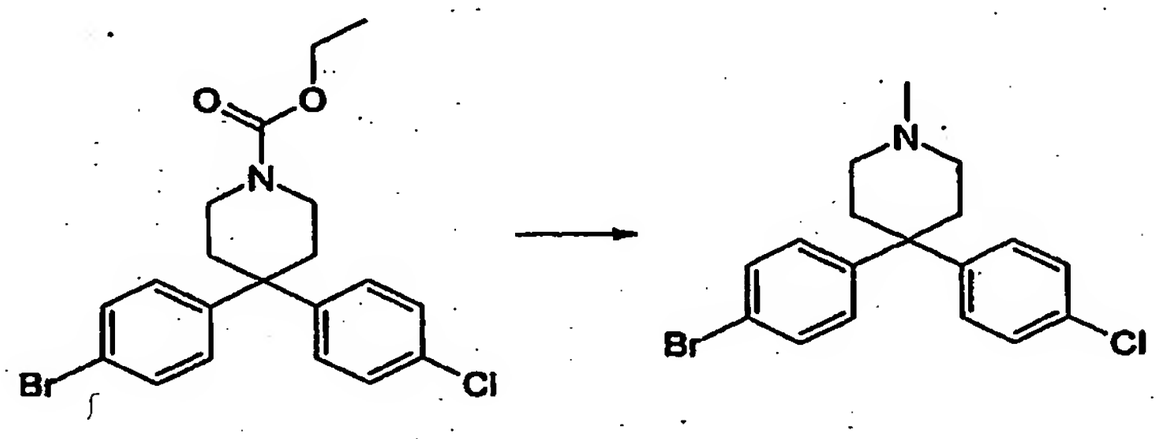
16A. 4-(4-Bromo-phenyl)-4-(4-chloro-phenyl)-piperidine-1-carboxylic acid ethyl ester



To a stirring suspension of 4-(4-Bromo-phenyl)-4-(4-chloro-phenyl)-piperidine* (0.28g, 0.80mmol) in dichloromethane (10ml), were added triethylamine (0.45ml, 3.2mmol) and ethyl chloroformate (0.085ml, 0.88mmol). The reaction mixture was stirred for 3 hours, diluted with ethyl acetate and washed with 1N HCl, saturated sodium hydrogen carbonate and brine. The organic layer was separated, dried ($MgSO_4$), filtered and concentrated to afford the title compound (0.29g, 94% yield). LCMS: (PS-A2), R_t 4.02 $[M+H]^+$ 422, 424.

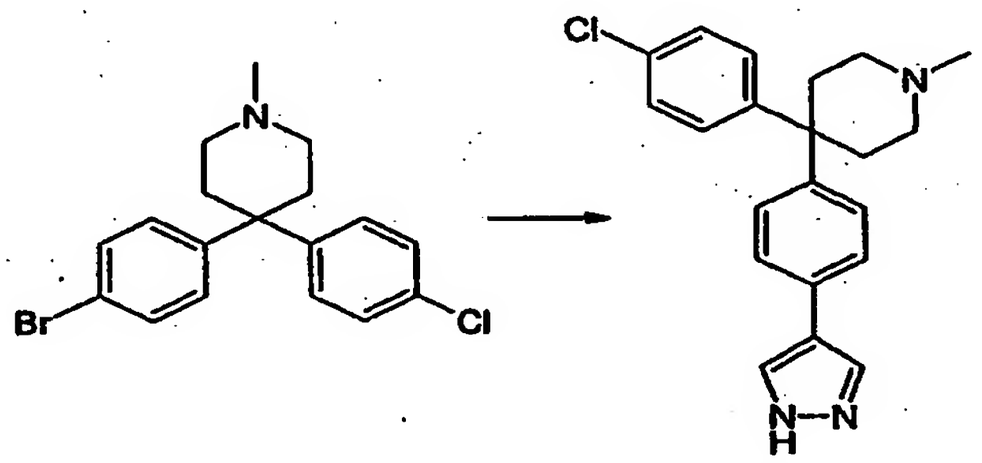
*This starting material can be made by the method described in Example 14A

16B. 4-(4-Bromo-phenyl)-4-(4-chloro-phenyl)-1-methyl-piperidine



Under a nitrogen atmosphere 4-(4-Bromo-phenyl)-4-(4-chloro-phenyl)-piperidine-1-carboxylic acid ethyl ester (0.28g, 0.66mmol) and lithium aluminum hydride (0.051g) were suspended in tetrahydrofuran (5ml) and stirred for 2 hours. The reaction mixture was quenched with addition of water, solvent removed under reduced pressure, the residue was partitioned between ethyl acetate and 2N NaOH. The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated to afford the desired product (0.241g, 99% yield). LC/MS: (PS-B3) R_t 3.78 $[M+H]^+$ 363.95, 365.73.

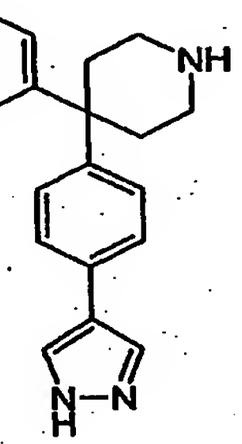
16C. 4-(4-Chloro-phenyl)-1-methyl-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine



4-(4-Bromo-phenyl)-4-(4-chloro-phenyl)-1-methyl-piperidine was reacted with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole following the procedure set out in Example 1 to give the title compound. LC/MS: (PS-B3) R_t 2.90 $[M+H]^+$ 352. ^1H NMR (Me-d_3-OD) δ 2.41-2.53 (2H, m), 2.82 (3H, d), 2.97-3.12 (4H, m), 3.56-3.59 (2H, m), 7.28 (2H, s), 7.34 (1H, m), 7.42 (1H, d), 7.49 (1H, d), 7.54 (1H, d), 7.61 (1H, d), 7.75 (1H, d), 8.52 (2H, d).

EXAMPLE 17

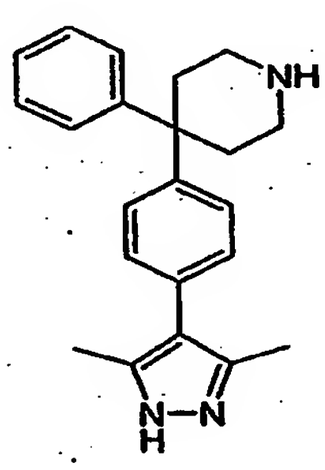
4-Phenyl-4-[4-(1H-pyrazol-4-yl)-phenyl]-piperidine



By following the procedure described in Example 1 but substituting 2-(4-chlorophenyl)-2-phenylethylamine hydrochloride for 4-(4-Chloro-phenyl)-4-phenyl-piperidine, the title compound was obtained. LC/MS: (PS-A2) R_t 1.88 $[M+H]^+$ 304. ^1H NMR (Me-d_3-OD) δ 2.65-2.71 (4H, m), 3.21 (4H, t), 7.18-7.22 (1H, m), 7.32-7.38 (6H, m), 7.55 (2H, d), 7.93 (2H, s).

EXAMPLE 18

4-[4-(3,5-Dimethyl-1H-pyrazol-4-yl)-phenyl]-4-phenyl-piperidine

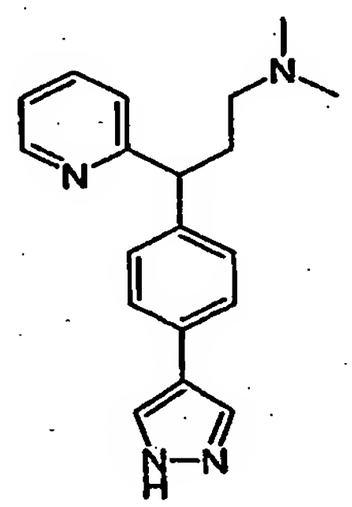


By following the procedure described in Example 1 but substituting 2-(4-chlorophenyl)-2-phenylethylamine hydrochloride and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole for 4-(4-Chloro-phenyl)-4-phenyl-piperidine and 3,5-dimethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole, the title compound was obtained. LC/MS: (PS-A2) R_t 2.95 $[M+H]^+$ 315.

^{1}H NMR (Me-d_3-OD) δ 2.22 (6H, s), 2.66-2.76 (4H, m), 3.16-3.28 (4H, m), 7.19-7.44 (9H, m).

EXAMPLE 19

Dimethyl-{3-[4-(1H-pyrazol-4-yl)-phenyl]-3-pyridin-2-yl-propyl}-amine

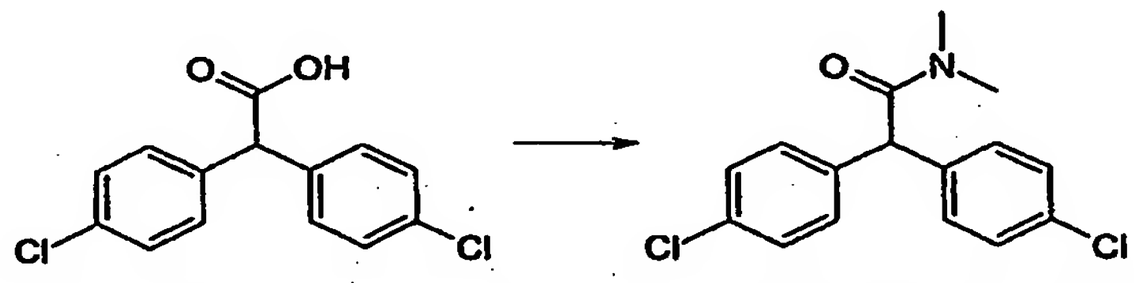


By following the procedure described in Example 1 but substituting 2-(4-chlorophenyl)-2-phenylethylamine hydrochloride for brompheniramine maleate, the title compound was obtained. LC/MS: (PS-B2) R_t 2.29 $[M+H]^+$ 307. ^{1}H NMR (Me-d_3-OD) δ 2.44-2.54 (1H, m), 2.59-2.70 (1H, m), 2.77 (6H, s), 2.93-3.01 (2H, m), 4.20 (1H, t), 7.25-7.28 (1H, m), 7.32-7.36 (3H, m), 7.54 (2H, d), 7.75 (1H, dt), 7.94 (2H, br s), 8.54 (2H, br d).

EXAMPLE 20

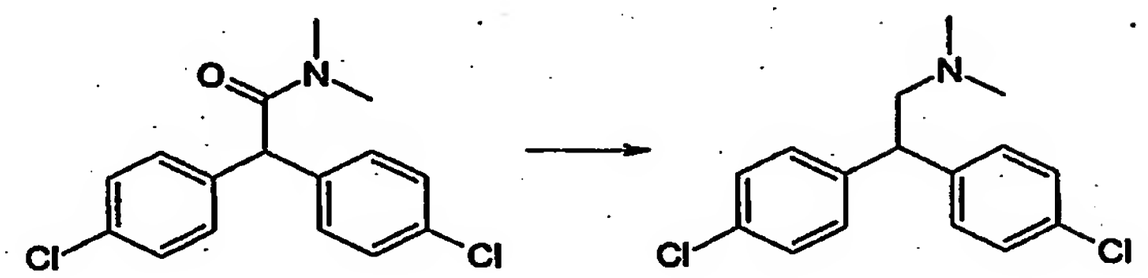
{2-(4-Chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-dimethyl-amine

20A. 2,2-Bis-(4-chloro-phenyl)-N,N-dimethyl-acetamide



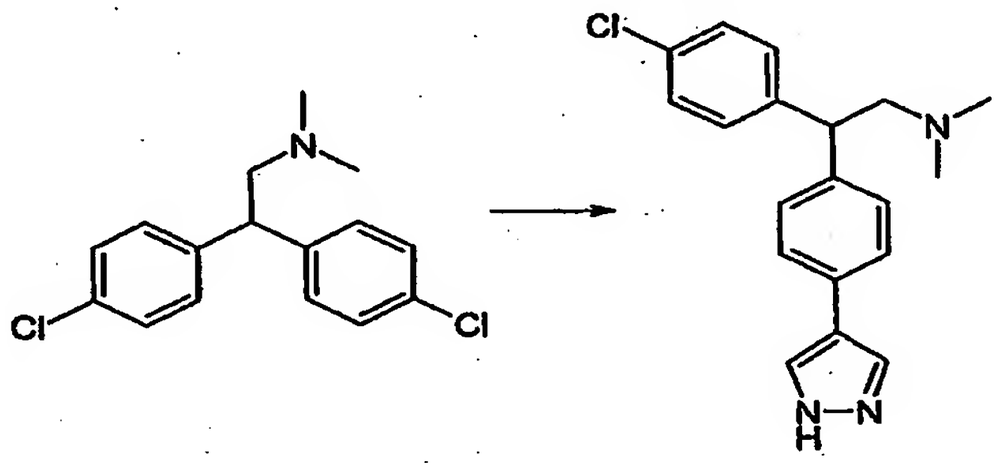
Bis-(4-chloro-phenyl)-acetic acid was reacted with dimethylamine following the procedure set out in Example 8D to give the title compound. LC/MS: (PS-A2) R_t 3.40 $[M+H]^+$ 309.95.

20B. [2,2-Bis-(4-chloro-phenyl)-ethyl]-dimethyl-amine



By following the procedure described in Example 8E but substituting 3-(4-Bromo-phenyl)-3-(4-chloro-phenyl)-N-methyl-propionamide for 2,2-Bis-(4-chloro-phenyl)-N,N-dimethyl-acetamide, the title compound was obtained. LC/MS: (PS-B2) R_t 3.75 $[M+H]^+$ 295.99.

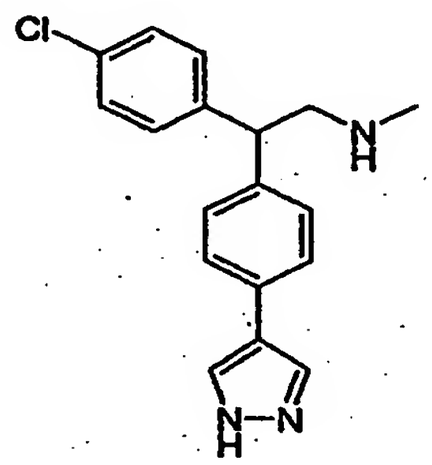
20C. {2-(4-Chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-dimethyl-amine



[2,2-Bis-(4-chloro-phenyl)-ethyl]-dimethyl-amine was reacted with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole following the procedure set out in Example 1 to give the title compound. LC/MS: (PS-B2) R_t 3.07 $[M+H]^+$ 325.99. ^{1}H NMR (Me-d_3-OD) δ 2.5 (6H, s), 4.34 (1H, t), 7.31-7.36 (6H, m), 7.50 (2H, d), 7.92 (2H, s).

EXAMPLE 21

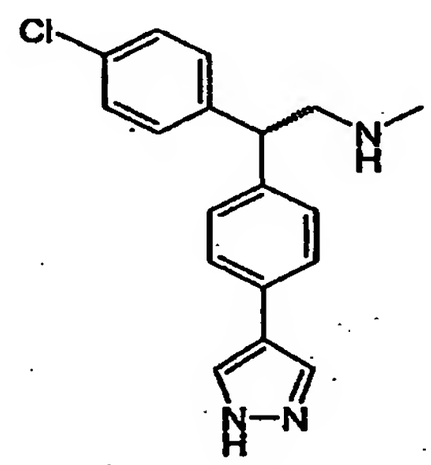
{2-(4-Chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-methyl-amine



By following the procedure described in Example 20 but substituting dimethylamine for methylamine, the title compound was obtained. LC/MS: (PS-B2) R_t 2.83 $[M+H]^+$ 312.07. ^1H NMR (Me-d_3-OD) δ 2.42 (3H, s), 3.20-3.23 (2H, dd), 4.18 (1H, t), 7.27-7.33 (6H, m), 7.54 (2H, d), 7.92 (2H, br s).

EXAMPLE 22

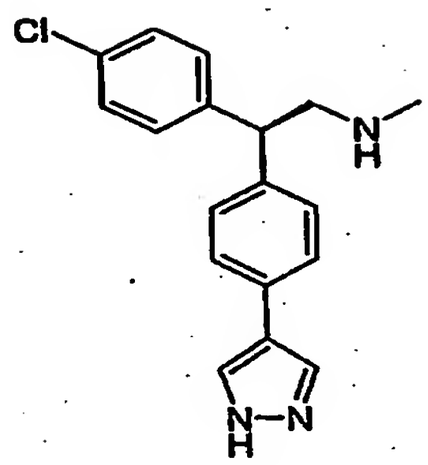
{2-(4-Chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-methyl-amine (R)



Prepared using the same procedure as Example 21 but enantiomers separated by chiral preparative HPLC using method AG-CP2. LCMS: (AG-CA) R_t 5.58min, 97.4%ee. ^1H NMR (Me-d_3-OD) δ 2.75 (3H, s), 3.78 (2H, d), 4.43 (1H, t), 7.39 (4H, s), 7.44 (2H, d), 7.69 (2H, d), 8.43 (2H, s).

EXAMPLE 23

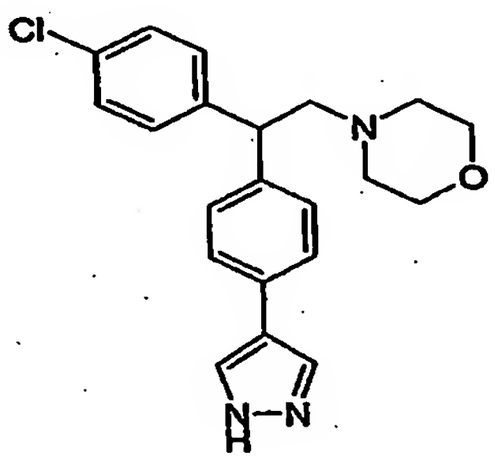
{2-(4-Chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-methyl-amine (S)



Prepared using the same procedure as Example 21 but enantiomers separated by chiral preparative HPLC using method AG-CP2. LCMS: (AG-CA) R_t 4.51min, 98.0%ee. ^{1}H NMR (Me-d_3-OD) δ 2.75 (3H, s), 3.79 (2H, d), 4.51 (1H, t), 7.37-7.43 (4H, m), 7.49 (2H, d), 7.73 (2H, d), 8.66 (2H, s).

EXAMPLE 24

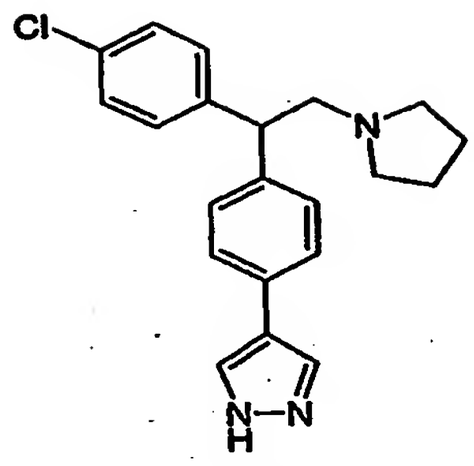
4-{2-(4-Chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-morpholine



By following the procedure described in Example 20 but substituting dimethylamine for morpholine, the title compound was obtained. LC/MS: (PS-B3) R_t 3.07 $[M+H]^+$ 368.05. ^{1}H NMR (Me-d_3-OD) δ 2.50 (4H, m), 2.97 (2H, m), 3.60 (4H, t), 4.26 (1H, t), 7.27 (6H, m). 7.49 (2H, d), 7.89 (2H, s).

EXAMPLE 25

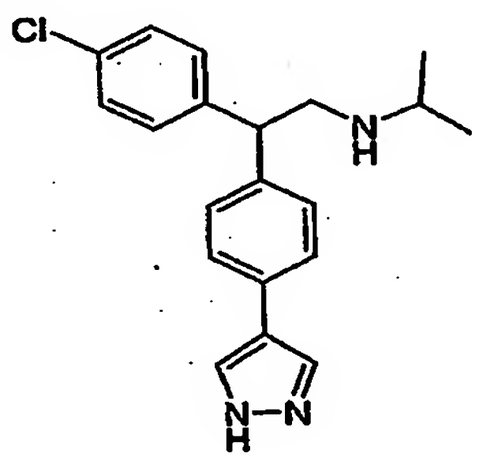
4-{4-[1-(4-Chloro-phenyl)-2-pyrrolidin-1-yl-ethyl]-phenyl}-1H-pyrazole



By following the procedure described in Example 20 but substituting dimethylamine for pyrrolidine, the title compound was obtained. LC/MS: (PS-A2) R_t 2.06 $[M+H]^+$ 354.01. ^1H NMR (Me-d_3-OD) δ 1.85 (4H, m), 2.87 (4H, m), 3.47 (2H, d), 4.31 (1H, t), 7.30-7.37 (6H, m), 7.54 (2H, d), 7.92 (2H, s).

EXAMPLE 26

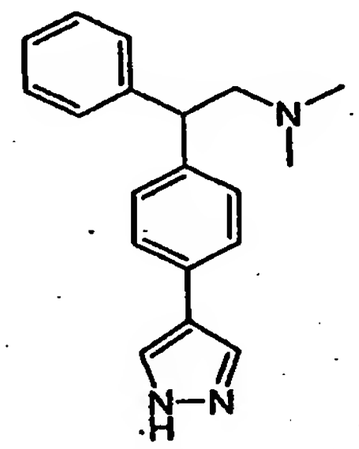
{2-(4-Chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-isopropyl-amine



By following the procedure described in Example 20 but substituting dimethylamine for isopropylamine, the title compound was obtained. LC/MS: (PS-A2) R_t 2.10 $[M+H]^+$ 340. ^1H NMR (Me-d_3-OD) δ 1.31 (6H, d), 3.38-3.45 (1H, m), 3.65-3.74 (2H, m), 4.39 (1H, br t), 7.37 (6H, m), 7.59 (2H, d), 7.94 (2H, s).

EXAMPLE 27

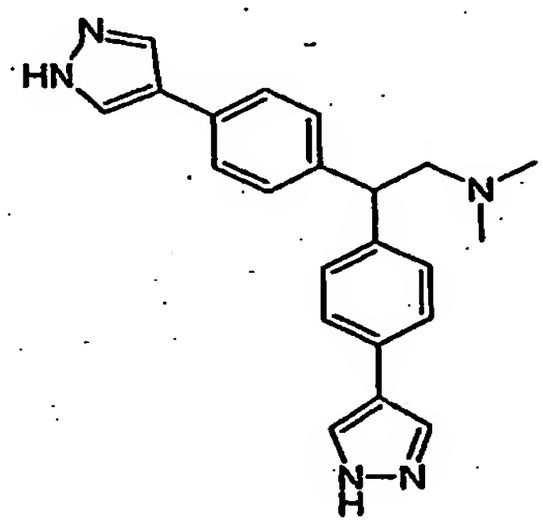
Dimethyl-{2-phenyl-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-amine



By following the procedure described in Example 20, the title compound was obtained. LC/MS: (PS-B2) R_t 2.82 $[M+H]^+$ 292.11. ^1H NMR (Me-d_3-OD) δ 2.25 (6H, s), 2.95-3.04 (2H, m), 4.20 (1H, t), 7.16 (1H, t), 7.26-7.33 (6H, m), 7.49 (2H, d), 7.89 (2H, s).

EXAMPLE 28

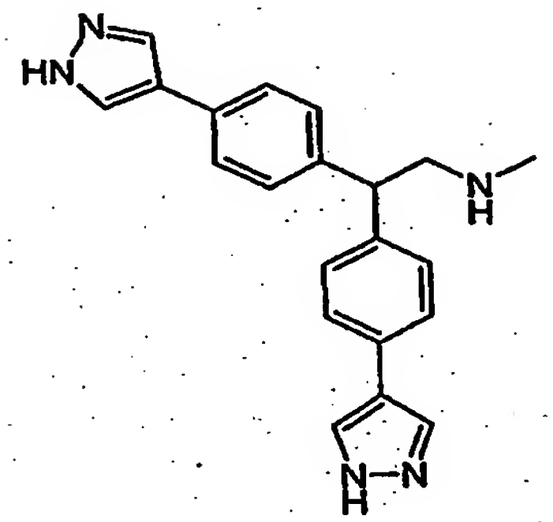
{2,2-Bis-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-dimethyl-amine



By following the procedure described in Example 20, the title compound was obtained. LC/MS: (PS-B2) R_t 2.45 $[M+H]^+$ 358.11. ^1H NMR (Me-d_3-OD) δ 2.69 (6H, s), 3.59 (2H, d), 4.43 (1H, t), 7.39 (4H, d), 7.57 (4H, d), 7.93 (4H, s).

EXAMPLE 29

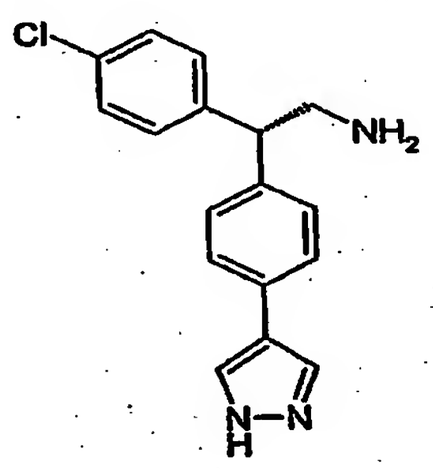
{2,2-Bis-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-methyl-amine



By following the procedure described in Example 21, the title compound was obtained. LC/MS: (PS-B2) R_t 2.18 $[M+H]^+$ 344.11. ^{1}H NMR (Me-d_3-OD) δ 2.65 (3H, s), 3.60 (2H, d), 4.34 (1H, t), 7.36 (4H, d), 7.59 (4H, d), 7.94 (4H, s).

EXAMPLE 30

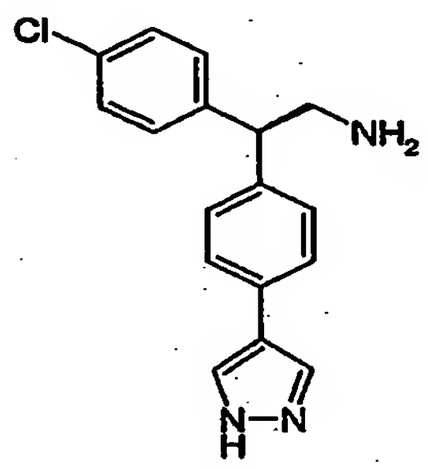
2-(4-Chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethylamine (R)



Prepared using the same procedure as Example 4 but enantiomers separated by chiral preparative HPLC using method AG-CP1. LCMS: (FL-C) R_t 10.97min, 95.7%ee. ^{1}H NMR (Me-d_3-OD) δ 3.65 (2H, m), 4.30 (1H, t), 7.35-7.40 (6H, m), 7.64 (2H, d), 8.16 (2H, s).

EXAMPLE 31

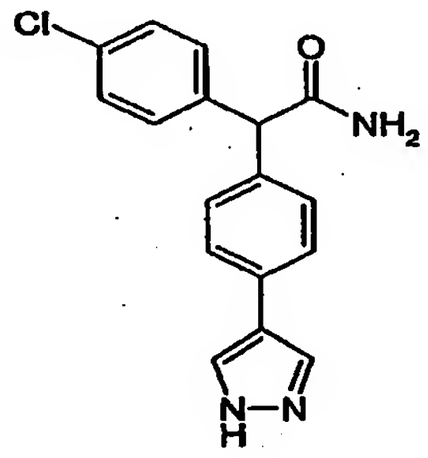
2-(4-Chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethylamine (S)



Prepared using the same procedure as Example 4 but enantiomers separated by chiral preparative HPLC using method AG-CP1. LCMS: (FL-C) R_t 9.63min, 100%ee. ^{1}H NMR (Me-d_3-OD) δ 3.66 (2H, m), 4.30 (1H, t), 7.35-7.40 (6H, m), 7.64 (2H, d), 8.15 (2H, s).

EXAMPLE 32

2-(4-Chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-acetamide

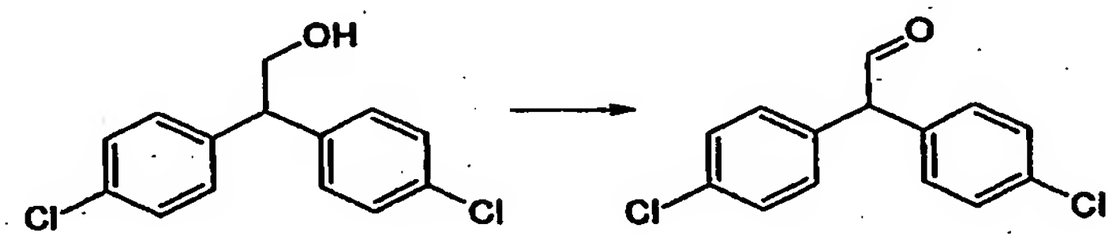


By following the procedure described in Example 12A followed by 12C but substituting 3-(4-Bromo-phenyl)-3-(4-chloro-phenyl)-propionic acid for Bis-(4-chloro-phenyl)-acetic acid, the title compound was obtained. LC/MS: (PS-A2) R_t 2.53 $[M+H]^+$ 312. ^{1}H NMR (Me-d_3-OD) δ 4.99 (1H, s), 7.30-7.33 (6H, m), 7.55 (2H, d), 7.86-8.02 (2H, br s).

EXAMPLE 33

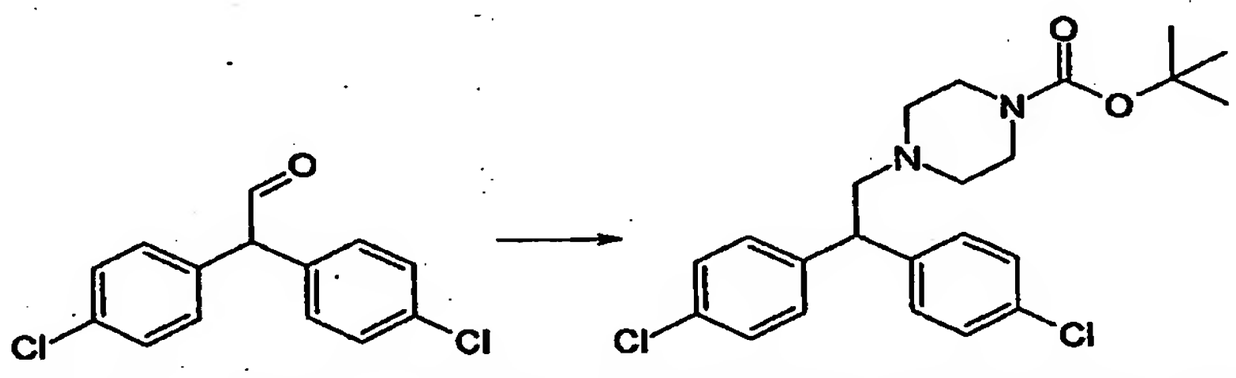
1-{2-(4-Chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-piperazine

37A. Bis-(4-chloro-phenyl)-acetaldehyde



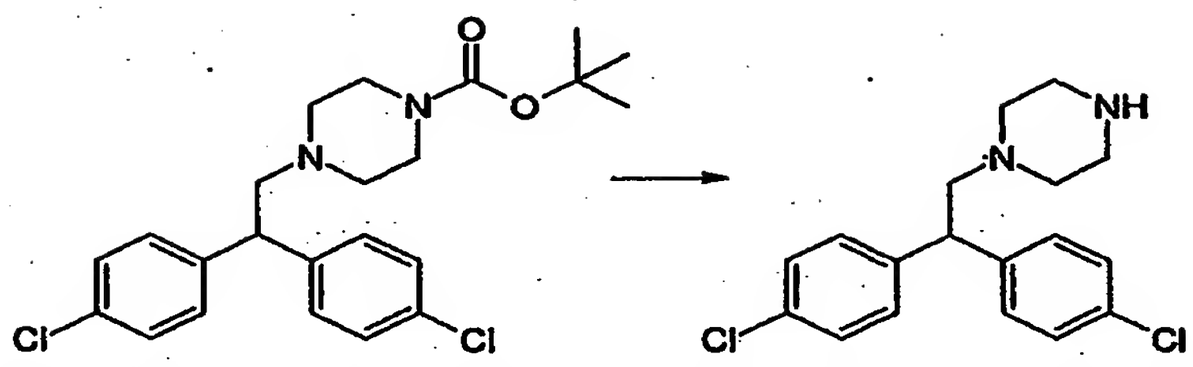
Dess-Martin periodinane (3.17g, 7.49mmol) was added to a solution of 2,2-Bis-(4-chloro-phenyl)-ethanol in dichloromethane (40ml). The reaction mixture was stirred at room temperature for 17 hours under nitrogen, 2N NaOH added (15ml) and the organic layer was separated, dried (MgSO4), filtered and concentrated to afford the title compounds which was used in the next step without further purification. LC/MS: (PS-B3) R_t 3.62 $[M+H]^+$ 262.91.

33B. 4-[2,2-Bis-(4-chloro-phenyl)-ethyl]-piperazine-1-carboxylic acid tert-butyl ester



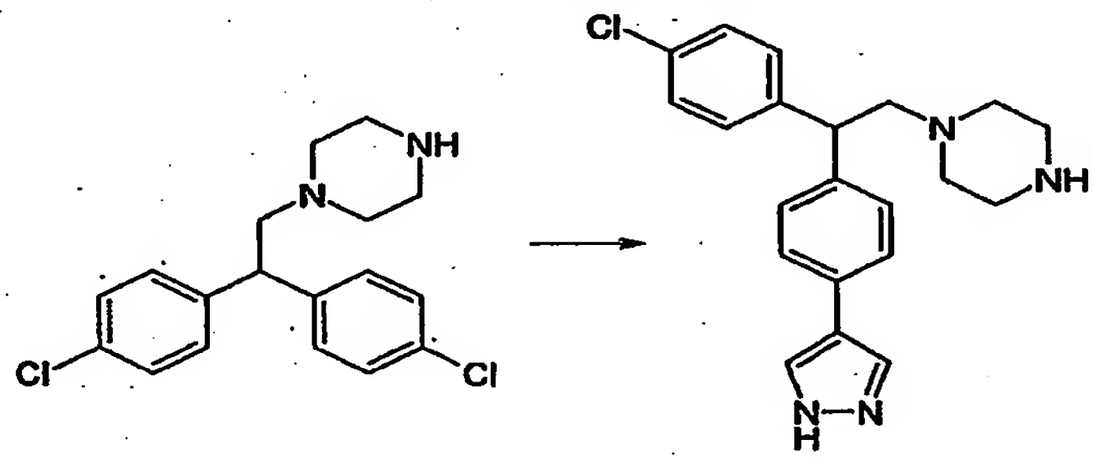
To a solution of bis-(4-chloro-phenyl)-acetaldehyde (3.74mmol) in methanol under a nitrogen atmosphere, N-BOC-piperazine (1.05g, 5.61mmol) was added ???, the reaction mixture was stirred for 1 hour before addition of sodium cyanoborohydride (0.28g, 4.49mmol). The reaction mixture was stirred for 18 hours, water added (3ml) and the solvent removed under reduced pressure. The residue was partitioned between dichloromethane and water, the organic layer was separated, dried (MgSO4), filtered and concentrated. Purified over flash silica chromatography eluting with ethyl acetate/petroleum ether (3:7) to yield the title compound (0.18g, 11% yield for steps 30A and 30B combined). LC/MS: (PS-A2) R_t 2.66 $[M\text{-}BOC+H]^+$ 335.02.

33C. 1-[2,2-Bis-(4-chloro-phenyl)-ethyl]-piperazine



4-[2,2-Bis-(4-chloro-phenyl)-ethyl]-piperazine-1-carboxylic acid tert-butyl ester was treated with HCl in ethyl acetate (saturated, 5ml) for 1 hour, solvent removed under reduced pressure to afford the title compound as the HCl salt

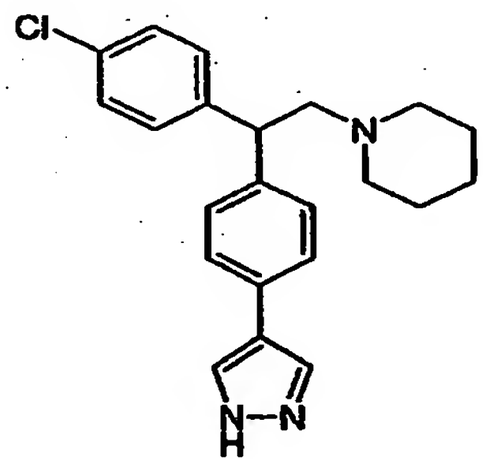
33D. 1-{2-(4-Chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-piperazine



1-[2,2-Bis-(4-chloro-phenyl)-ethyl]-piperazine was reacted with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole following the procedure set out in Example 1 to give the title compound. LC/MS: (PS-B3) R_t 2.63 $[M+H]^+$ 326.00. ^1H NMR (Me-d_3-OD) δ 3.55-3.68 (8H, m), 3.74 (1H, t), 4.10-4.17 (2H, m), 7.39 (2H, d), 7.48 (2H, d), 7.54 (2H, d), 7.70 (2H, d), 8.57 (2H, br s).

EXAMPLE 34

1-{2-(4-Chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethyl}-piperidine



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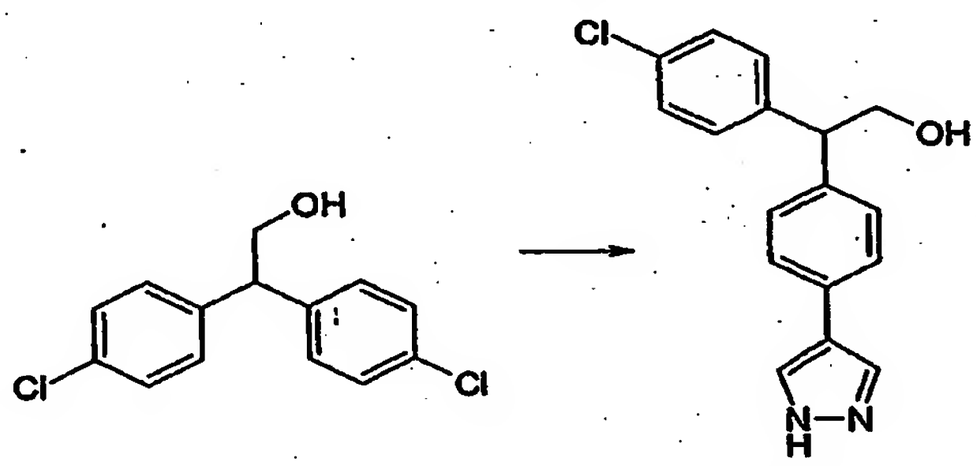
By following the procedure described in Example 33A, 33B and 33D but substituting piperidine for N-BOC-piperazine, the title compound was obtained. LC/MS: (PS-A2) R_t 2.21 $[M+H]^+$ 366.09. ^1H NMR (Me-d_3-OD) δ 1.44 (2H, m), 1.53 (4H, m), 2.39-2.57 (4H, m), 2.94-3.09 (2H, m), 4.26 (1H, t), 7.22-7.35 (6H, m), 7.50 (2H, d), 7.91 (2H, s).

EXAMPLE 35

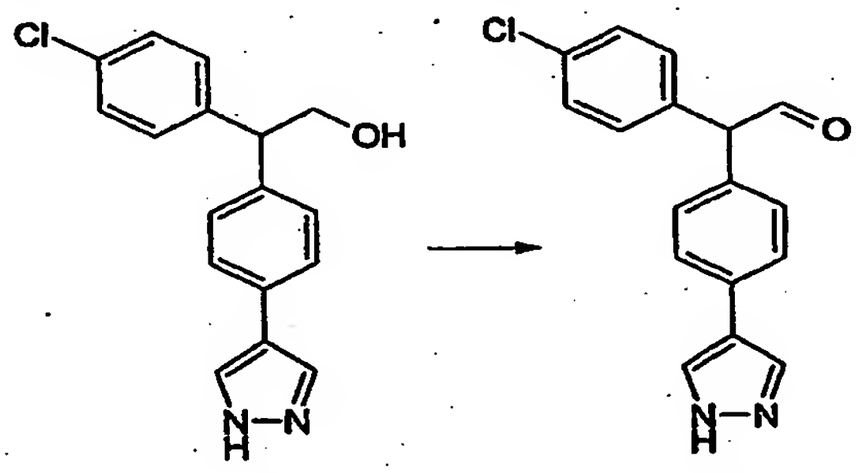
4-{4-[2-Azetidin-1-yl-1-(4-chloro-phenyl)-ethyl]-phenyl}-1H-pyrazole

35A. 2-(4-Chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethanol



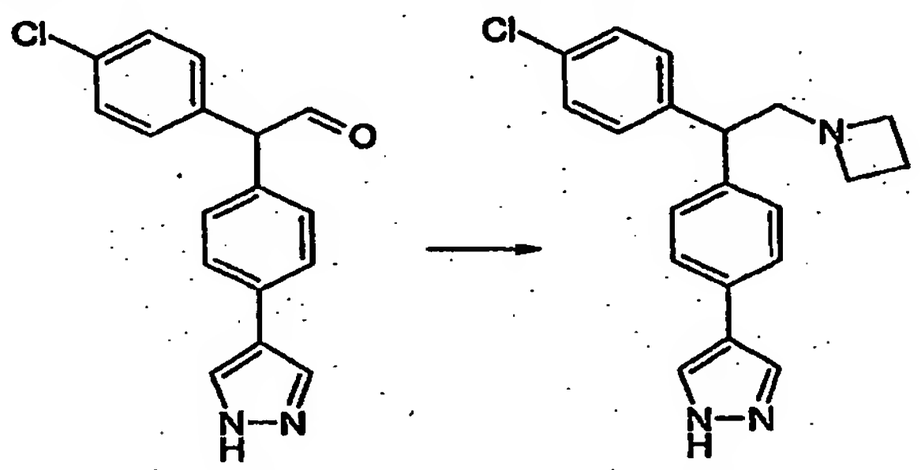
2,2-Bis-(4-chloro-phenyl)-ethanol was reacted with 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole following the procedure set out in Example 1 to give the title compound. LC/MS: (PS-A2) R_t 2.72 $[M+H]^+$ 299.00.

35B. (4-Chloro-phenyl)-[4-(1H-pyrazol-4-yl)-phenyl]-acetaldehyde



By following the procedure described in Example 33A but substituting 2,2-Bis-(4-chloro-phenyl)-ethanol for 2-(4-Chloro-phenyl)-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethanol, the title compound was obtained. LC/MS: (PS-B3) R_t 2.97 $[M+H]^+$ 294.98.

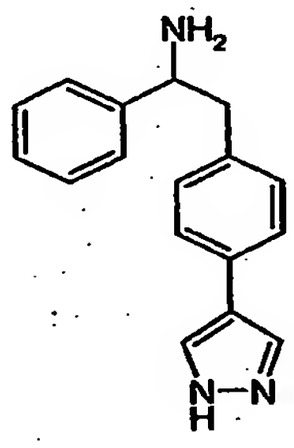
35C. 4-{4-[2-Azetidin-1-yl-1-(4-chloro-phenyl)-ethyl]-phenyl}-1H-pyrazole



By following the procedure described in Example 33B but replacing bis-(4-chloro-phenyl)-acetaldehyde and N-BOC-piperazine with (4-Chloro-phenyl)-[4-(1H-pyrazol-4-yl)-phenyl]-acetaldehyde and azetidine, the title compound was obtained. LC/MS: (PS-B3) R_t 2.99 $[M+H]^+$ 338.09. ^1H NMR (Me-d_3-OD) δ 3.57-3.60 (1H, m), 3.63-3.70 (2H, m), 3.71-3.77 (1H, m), 4.01 (2H, m), 4.14 (2H, m), 4.40 (1H, t), 7.40 (4H, br s), 7.49 (2H, d), 7.73 (2H, d), 8.69 (2H, br s).

EXAMPLE 36

1-Phenyl-2-[4-(1H-pyrazol-4-yl)-phenyl]-ethylamine

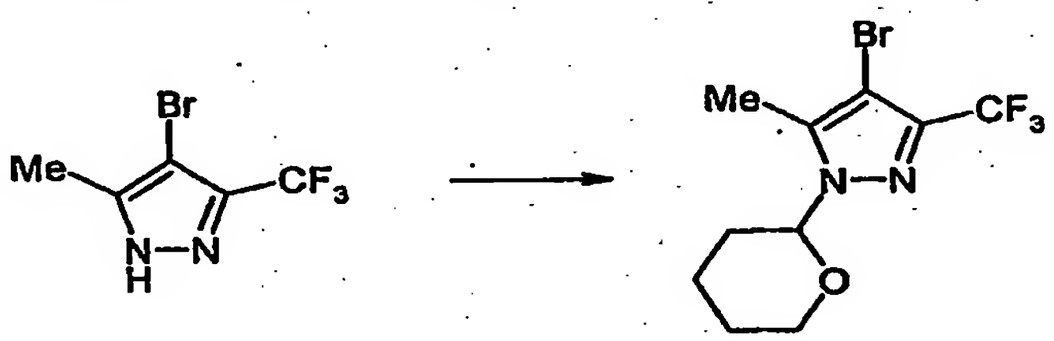


By following the procedure described in Example 5 but replacing 3-bromobenzylmagnesium bromide and 3,5-dimethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole with 4-bromobenzylmagnesium bromide and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole, the title compound was obtained. LC/MS: (PS-B2) R_t 2.44 $[M+H]^+$ 264.04. ^1H NMR (Me-d_3-OD) δ 2.99 (2H, d), 4.13 (1H, t), 7.10 (2H, d), 7.20-7.38 (5H, m), 7.45 (2H, d), 7.91 (2H, s).

EXAMPLE 37

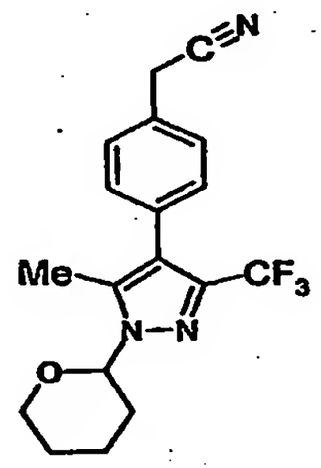
[4-(5-Methyl-3-trifluoromethyl-1H-pyrazol-4-yl)-phenyl]-acetonitrile

37A. 4-Bromo-5-methyl-1-(tetrahydro-pyran-2-yl)-3-trifluoromethyl-1H-pyrazole



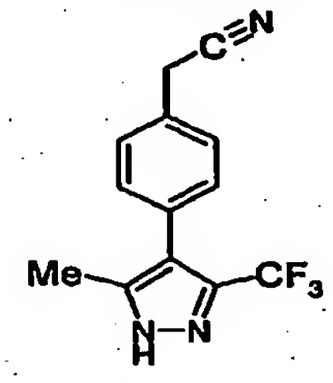
To a solution of 4-bromo-5-methyl-3-trifluoromethyl-1H-pyrazole (1.4 g, 6.2 mmol, 1.0 equiv) in chloroform (31 ml) was added p-toluene sulphonic acid monohydrate (118 mg, 0.62 mmol, 0.1 equiv). The solution was cooled to 0 °C and 3,4-dihydro-2H-pyran (0.85 ml, 9.3 mmol, 1.5 equiv) was added drop-wise over 5 minutes. The mixture was allowed to warm to room temperature for 1 hour and the solvents were removed under reduced pressure. The crude mixture was purified by column chromatography (SiO_2), eluting with 0→25% EtOAc-petrol over a linear gradient to afford the title compound 1.4 g (59%), LCMS (PS-A) R_t 3.72 min; *m/z* $[M+H]^+$ 314.

37B. {4-[5-Methyl-1-(tetrahydro-pyran-2-yl)-3-trifluoromethyl-1H-pyrazol-4-yl]-phenyl}-acetonitrile



The product of Example 37A, 4-bromo-5-methyl-1-(tetrahydro-pyran-2-yl)-3-trifluoromethyl-1H-pyrazole, was reacted with 4-(cyanomethylphenyl)boronic acid (Combi-Blocks, San Diego, USA Cat. No. 2444-001), under the conditions described in Example 1, to give the title compound.

37C. [4-(5-Methyl-3-trifluoromethyl-1H-pyrazol-4-yl)-phenyl]-acetonitrile



To {4-[5-Methyl-1-(tetrahydro-pyran-2-yl)-3-trifluoromethyl-1H-pyrazol-4-yl]-phenyl}-acetonitrile (Example 8B) (35 mg, 0.1 mmol, 1.0 equiv) in ethyl acetate (1 ml) was added HCl in ethyl acetate (1 ml) and the mixture was stirred for 1 hour. The solvents were removed under reduced pressure and the title compound was purified by column chromatography (SiO_2) eluting with a linear gradient (0→30% ethyl acetate-petrol) 16 mg (60%); LCMS (PS-A) R_t 2.85 min; *m/z* $[M+H]^+$ 266.

37D. Preparation of Compounds of the Formula (I) from [4-(5-Methyl-3-trifluoromethyl-1H-pyrazol-4-yl)-phenyl]-acetonitrile

(i) The product of Example 37B can be reacted with benzaldehyde under the conditions described in Example 2 to give 2-[4-(5-methyl-1-(tetrahydro-pyran-2-yl)-3-trifluoromethyl-1H-pyrazol-4-yl)-phenyl]-3-phenyl-propionitrile which can be deprotected by removal of the 1-tetrahydropyranyl group under the conditions set out in Example 37C to give 2-[4-(5-methyl-3-trifluoromethyl-1H-pyrazol-4-yl)-phenyl]-3-phenyl-propionitrile.

2-[4-(5-Methyl-3-trifluoromethyl-1H-pyrazol-4-yl)-phenyl]-3-phenyl-propionitrile or its 1-tetrahydropyranyl derivative can be reduced according to the method of Example 6 (and thereafter where necessary deprotected according to the method of Example 41C) to give 2-[4-(5-methyl-3-trifluoromethyl-1H-pyrazol-4-yl)-phenyl]-3-phenyl-propylamine.

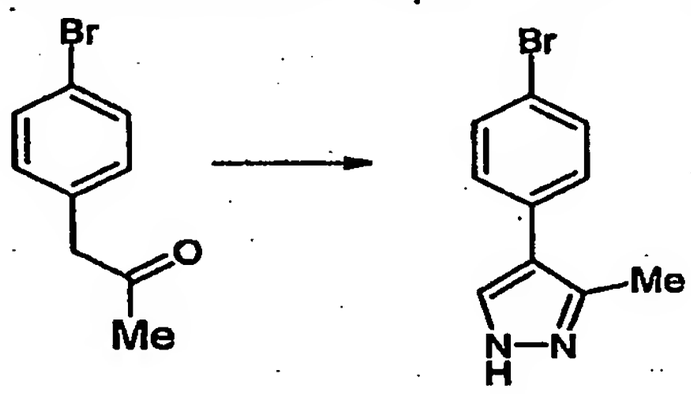
The product of Example 37B can also be reacted with benzyl magnesium bromide or phenyl magnesium bromide under the Grignard reaction conditions described in Example 5 to give (following deprotection by the method of Example 37C)

1-benzyl-2-[4-(5-methyl-3-trifluoromethyl-1H-pyrazol-4-yl)-phenyl]-ethylamine and 2-[4-(5-methyl-3-trifluoromethyl-1H-pyrazol-4-yl)-phenyl]-1-phenyl-ethylamine respectively.

EXAMPLE 38

Construction of Pyrazole Ring System

38A. Synthesis of 4-(4-Bromo-phenyl)-3-methyl-1H-pyrazole



To 4-bromophenylacetone (5.0 g, 23.5 mmol, 1.0 equiv) (Acros Organics 34216) was added N,N-dimethylformamide dimethyl acetal (11.3 ml, 84.6 mmol, 3.6 equiv) and the mixture was heated to 90 °C for 6 hours. The solvents were removed and the resulting gum was dissolved in ethanol (235 ml) with additional heating. Hydrazine hydrate (1.37 ml, 28.2 mmol, 1.2 equiv) was added and the mixture was heated to reflux for 15 hours. The solvents were removed under reduced pressure and the solid was triturated with dichloromethane to afford the title compound, 2.24 g (40%); LCMS (PS-A) R_t 2.87 min; *m/z* $[M+H]^+$ 238. Further material could be isolated from the mother liquor.

38B. Conversion of 4-(4-Bromo-phenyl)-3-methyl-1H-pyrazole to compounds of the Formula (I)

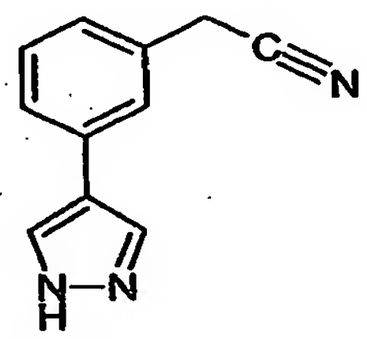
(i) 4-(4-Bromo-phenyl)-3-methyl-1H-pyrazole can be protected at the 1-position of the pyrazole ring by formation of the tetrahydropyranyl (THP) derivative by following the procedure set out in Example 38A. A Grignard reagent can then be prepared from the bromo-phenyl moiety by treating the protected derivative with magnesium in an ether solvent in standard fashion (see J. March, *Advanced Organic* Chemistry, 4th Edition, 1992, John Wiley, New York, pages 622-625). The Grignard reagent can be reacted with nitrostyrene (the

nitrostyrene having been prepared by a standard method such as the method described in *Organic Syntheses*, Collective Volume 1, page 413) and the resulting nitroethyl compound reduced to give 2-{4-[3-methyl-1-(tetrahydro-pyran-2-yl)-1H-pyrazol-4-yl]-phenyl}-2-phenyl-ethylamine. Removal of the tetrahydropyranyl group using the method of Example 8C gives 2-{4-[3-methyl-1H-pyrazol-4-yl]-phenyl}-2-phenyl-ethylamine.

(ii) The bromo-compound of Example 38A can be converted into compounds of the formula (I) in which the group A contains a nitrogen atom which is attached to the group E. The introduction of a nitrogen containing entity can be accomplished by reaction of the compound of Example 38A with [3-(4-chloro-phenylamino)-propyl]-methyl-carbamic acid tert-butyl ester under palladium catalysed amination conditions of the type described in *Organic Letters*, 2002, vol. 4, No. 17, pp2885-2888, followed by removal of the *t*-butyloxycarbonyl protecting group by standard methods.

EXAMPLE 39

[3-(1H-Pyrazol-4-yl)-phenyl]-acetonitrile



By following the procedure set out in Example 1 but using 3-bromophenyl-acetonitrile instead of 2-(4-chlorophenyl)-2-phenylethylamine, the title compound was obtained. LCMS (PS-A) 2.35 min; *m/z* $[M+H]^+$ 184.

3-(1H-Pyrazol-4-yl)-phenyl]-acetonitrile can be used as an intermediate in the preparation of compounds of the formula (I), for example by means of an aldehyde condensation reaction as described in Example 2 or a Grignard reaction as described in Example 5.

BIOLOGICAL ACTIVITY

EXAMPLE 40

Measurement of PKA Kinase Inhibitory Activity (IC_{50})

Compounds of the invention can be tested for PK inhibitory activity using the PKA catalytic domain from Upstate Biotechnology (#14-440) and the 9 residue PKA specific peptide (GRTGRRNSI), also from Upstate Biotechnology (#12-257), as the substrate. A final concentration of 1 nM enzyme is used in a buffer that includes 20 mM MOPS pH 7.2, 40 μM ATP/γ^{33}P-ATP and 50 mM substrate. Compounds are added in dimethylsulphoxide (DMSO) solution to a final DMSO concentration of 2.5%. The reaction is allowed to proceed for 20 minutes before addition of excess orthophosphoric acid to quench activity. Unincorporated γ^{33}P-ATP is then separated from phosphorylated proteins on a Millipore MAPH filter plate. The plates are washed, scintillant is added and the plates are then subjected to counting on a Packard Topcount.

The % inhibition of the PKA activity is calculated and plotted in order to determine the concentration of test compound required to inhibit 50% of the PKB activity (IC_{50}).

The compounds of Examples 1 and 4 have IC_{50} values of less than 1μM whereas the compounds of Examples 5 and 7 have IC_{50} values of less than 15μM.

EXAMPLE 41

Measurement of PKB Kinase Inhibitory Activity (IC_{50})

The inhibition of protein kinase B (PKB) activity by compounds can be determined determined essentially as described by Andjelkovic *et al.* (Mol. Cell. Biol. 19, 5061-5072 (1999)) but using a fusion protein described as PKB-PIF and described in full by Yang et al (Nature Structural Biology 9, 940 – 944 (2002)). The protein is purified and activated with PDK1 as described by Yang *et al.* The peptide AKTide-2T (H-A-R-K-R-E-R-T-Y-S-F-G-H-H-A-OH) obtained from Calbiochem (#123900) is used as a substrate. A final concentration of 0.6 nM enzyme is used in a buffer that includes 20 mM MOPS pH 7.2, 30 μM ATP/γ^{33}P-

ATP and 25 μM substrate. Compounds are added in DMSO solution to a final DMSO concentration of 2.5%. The reaction is allowed to proceed for 20 minutes before addition of excess orthophosphoric acid to quench activity. The reaction mixture is transferred to a phosphocellulose filter plate where the peptide binds and the unused ATP is washed away. After washing, scintillant is added and the incorporated activity measured by scintillation counting.

The % inhibition of the PKB activity is calculated and plotted in order to determine the concentration of test compound required to inhibit 50% of the PKB activity (IC_{50}).

Following the protocol described above, the IC_{50} values of the compounds of Examples 1, 4, 8-10, 12-17, 20-23, 25-31 and 33-35 have been found to be less than 1 μM whilst the compounds of Examples 2, 3, 5, 6, 7, 11, 18, 19, 24, 32 and 36 each have IC_{50} values of less than 5 μM.

PHARMACEUTICAL FORMULATIONS

EXAMPLE 42

(i) Tablet Formulation

A tablet composition containing a compound of the formula (I) is prepared by mixing 50 mg of the compound with 197mg of lactose (BP) as diluent, and 3 mg magnesium stearate as a lubricant and compressing to form a tablet in known manner..

(ii) Capsule Formulation

A capsule formulation is prepared by mixing 100mg of a compound of the formula (I) with 100mg lactose and filling the resulting mixture into standard opaque hard gelatin capsules.

Equivalents

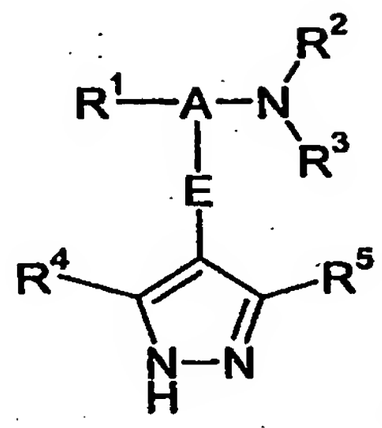
The foregoing examples are presented for the purpose of illustrating the invention and should not be construed as imposing any limitation on the scope of the invention. It will readily be apparent that numerous modifications and alterations

may be made to the specific embodiments of the invention described above and illustrated in the examples without departing from the principles underlying the invention. All such modifications and alternations are intended to be embraced by this application.

5

CLAIMS

1. A compound of the formula (I):



(I)

wherein A is a saturated hydrocarbon linker group containing from 1 to 7 carbon atoms, the linker group having a maximum chain length of 5 atoms extending between R^1 and NR^2R^3 and a maximum chain length of 4 atoms extending between E and NR^2R^3, wherein one of the carbon atoms in the linker group may optionally be replaced by an oxygen or nitrogen atom; and wherein the carbon atoms of the linker group A may optionally bear one or more substituents selected from oxo, fluorine and hydroxy, provided that the hydroxy group when present is not located at a carbon atom α with respect to the NR^2R^3 group and provided that the oxo group when present is located at a carbon atom α with respect to the NR^2R^3 group;

E is a monocyclic or bicyclic carbocyclic or heterocyclic group;

R^1 is an aryl or heteroaryl group;

R^2 and R^3 are independently selected from hydrogen, C_{1-4} hydrocarbyl and C_{1-4} acyl;

or R^2 and R^3 together with the nitrogen atom to which they are attached form a saturated monocyclic heterocyclic group having 4-7 ring members and optionally containing a second heteroatom ring member selected from O and N;

or one of R^2 and R^3 together with the nitrogen atom to which they are attached and one or more atoms from the linker group A form a saturated monocyclic heterocyclic group having 4-7 ring members and

optionally containing a second heteroatom ring member selected from O and N;

or NR^2R^3 and the carbon atom of linker group A to which it is attached together form a cyano group;

R^4 is selected from hydrogen, halogen, C_{1-5} saturated hydrocarbyl, cyano and CF_3; and

R^5 is selected from selected from hydrogen, C_{1-5} saturated hydrocarbyl, cyano, $CONH_2$, $CONHR^9$, CF_3, NH_2, $NHCOR^9$ or $NHCONHR^9$;

R^9 is phenyl or benzyl each optionally substituted by one or substituents selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

X^1 is O, S or NR^c and X^2 is =O, =S or =NR^c.

2. A compound according to claim 1 wherein A is a saturated hydrocarbon linker group containing from 1 to 7 carbon atoms, the linker group having a maximum chain length of 5 atoms extending between R^1 and NR^2R^3 and a maximum chain length of 4 atoms extending between E and NR^2R^3, wherein one of the carbon atoms in the linker group may optionally be replaced by an oxygen or nitrogen atom; and wherein the carbon atoms of the linker group A may optionally bear one or more substituents selected

from fluorine and hydroxy, provided that the hydroxy group when present is not located at a carbon atom α with respect to the NR^2R^3 group; and

R^5 is selected from selected from hydrogen, C_{1-5} saturated hydrocarbyl, cyano, $CONH_2$, CF_3, NH_2, $NHCOR^9$ and $NHCONHR^9$.

3. A compound according to claim 1 or claim 2 wherein the linker group A has a maximum chain length of 3 atoms (more preferably 1 or 2 atoms, and most preferably 2 atoms) extending between R^1 and NR^2R^3.

4. A compound according to any one of claims 1 to 3 wherein the linker group A has a maximum chain length of 3 atoms extending between E and NR^2R^3.

5. A compound according to claim 4 wherein the linker group A has a chain length of 2 or 3 atoms extending between R^1 and NR^2R^3 and a chain length of 2 or 3 atoms extending between E and NR^2R^3.

6. A compound according to any one of the preceding claims wherein the linker group atom linked directly to the group E is a carbon atom and the linker group A has an all-carbon skeleton.

7. A compound according to any one of the preceding claims wherein the moiety R^1-A-NR^2R^3 is represented by the formula R^1-$(G)_k$-$(CH_2)_m$-X-$(CH_2)_n$-$(CR^6R^7)_p$-NR^2R^3 wherein G is NH, NMe or O; X is attached to the group E and is selected from $(CH_2)_j$-CH, $(CH_2)_j$-N and $(NH)_j$-CH; j is 0 or 1, k is 0 or 1, m is 0 or 1, n is 0, 1, 2, or 3 and p is 0 or 1, and the sum of j, k, m, n and p does not exceed 4; and R^6 and R^7 are the same or different and are selected from methyl and ethyl, or CR^6R^7 forms a cyclopropyl group.

8. A compound according to claim 7 wherein k is 0, m is 0 or 1, n is 0, 1,2 or 3 and p is 0.

9. A compound according to claim 7 wherein k is 0, m is 0 or 1, n is 0, 1 or 2 and p is 1.

10. A compound according to claim 7 wherein X is $(CH_2)_j$-CH, k is 1, m is 0, n is 0, 1,2 or 3 and p is 0.

11. A compound according to claim 7 wherein X is $(CH_2)_j$-CH, k is 1, m is 0, n is 0, 1 or 2 and p is 1.

12. A compound according to any one of claims 7, 10 and 11 wherein j is 0.

13. A compound according to any one of claims 7, 10 and 11 wherein j is 1.

14. A compound according to any one of claims 7, 9 and 11 wherein CR^6R^7 is $C(CH_3)_2$.

15. A compound according to claim 7 wherein the portion R^1-A-NR^2R^3 of the compound is represented by the formula R^1-X-$(CH_2)_n$-NR^2R^3 where X is attached to the group E and is a group CH, and n is 2.

16. A compound according to claim 1or claim 2 wherein R^1-A(E)-NR^2R^3 is a group selected from the groups A1 to A11 set out in Table 1 herein.

17. A compound according to claim 16 wherein R^1-A(E)-NR^2R^3 is selected from groups A1, A2, A3 and A10 in Table 1.

18. A compound according to claim 17 wherein R^1-A(E)-NR^2R^3 is the group A10 in Table 1.

19. A compound according to any one of the preceding claims wherein E is a monocyclic group.

20. A compound according to any one of the preceding claims wherein E is an aryl or heteroaryl group.

21. A compound according to claim 20 wherein E is selected from optionally substituted phenyl, thiophene, furan, pyrimidine and pyridine groups.

22. A compound according to claim 21 wherein E is a phenyl group.

23. A compound according to any one of claims 1 to 19 wherein E is a non-aromatic monocyclic group selected from cycloalkanes such as cyclohexane and cyclopentane, and nitrogen-containing rings such as piperazine and piperazone.

24. A compound according to any one of the preceding claims wherein the group A and the pyrazole group are attached to the group E in a *meta* or *para* relative orientation; i.e. A and the pyrazole group are not attached to adjacent ring members of the group E.

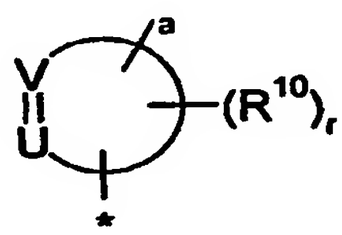
25. A compound according to claim 24 wherein E is selected from 1,4-phenylene, 1,3-phenylene, 2,5-pyridylene and 2,4-pyridylene, 1,4-piperazinyl, and 1,4-piperazonyl.

26. A compound according to any one of the preceding claims wherein E is unsubstituted or has up to 4 substituents R^8 selected from hydroxy, oxo (when E is non-aromatic), chlorine, bromine, trifluoromethyl, cyano, C_{1-4} hydrocarbyloxy and C_{1-4} hydrocarbyl optionally substituted by C_{1-2} alkoxy or hydroxy.

27. A compound according to claim 26 wherein E has 0-3 substituents, more preferably 0-2 substituents, for example 0 or 1 substituent.

28. A compound according to claim 27 wherein E is unsubstitituted.

29. A compound according to any one of the preceding claims wherein the group E is an aryl or heteroaryl group having five or six members and containing up to three heteroatoms selected from O, N and S, the group E being represented by the formula:



where * denotes the point of attachment to the pyrazole group, and "a" denotes the attachment of the group A;

r is 0, 1 or 2;

U is selected from N and CR^{12a}; and

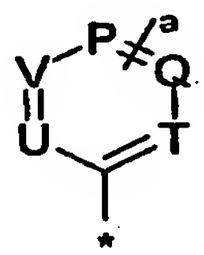
V is selected from N and CR^{12b}; where R^{12a} and R^{12b} are the same or different and each is hydrogen or a substituent containing up to ten atoms selected from C, N, O, F, Cl and S provided that the total number of non-hydrogen atoms present in R^{12a} and R^{12b} together does not exceed ten; or R^{12a} and R^{12b} together with the carbon atoms to which they are attached form an unsubstituted five or six membered saturated or unsaturated ring containing up to two heteroatoms selected from O and N; and

R^{10} is selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$;

R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

X^1 is O, S or NR^c and X^2 is =O, =S or =NR^c.

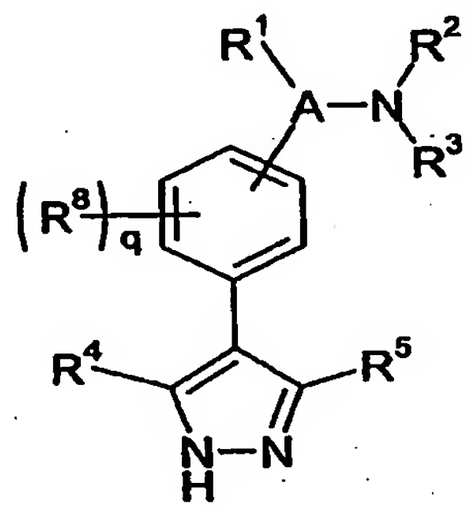
30. A compound according to claim 29 wherein E is represented by the formula:



where P, Q and T are the same or different and are selected from N, CH and NCR^{10}, provided that the group A is attached to a carbon atom.

31. A compound according to claim 30 wherein the group E is selected from groups B1 to B13 in Table 2.

32. A compound according to claim 22 having the formula (II):



(II)

wherein the group A is attached to the *meta* or *para* position of the benzene ring and q is 0-4.

33. A compound according to claim 32 wherein q is 0, 1 or 2, preferably 0 or 1 and most preferably 0.

34. A compound according to any one of the preceding claims wherein R^1 is selected from phenyl, naphthyl, thienyl, furan, pyrimidine and pyridine.

35. A compound according to claim 34 wherein R^1 is phenyl.

36. A compound according to any one of the preceding claims wherein R^1 is unsubstituted or is substituted by up to 5 substituents selected from hydroxy; C_{1-4} acyloxy; fluorine; chlorine; bromine; trifluoromethyl; cyano;

C_{1-4} hydrocarbyloxy and C_{1-4} hydrocarbyl optionally substituted by C_{1-2} alkoxy or hydroxy; and five membered heteroaryl groups containing one or two heteroatoms selected from N, O and S, the heteroaryl groups being optionally substituted by one or more C_{1-4} alkyl substituents.

37. A compound according to claim 36 wherein R^1 is unsubstituted or is substituted by up to 5 substituents selected from hydroxy, C_{1-4} acyloxy, fluorine, chlorine, bromine, trifluoromethyl, cyano, C_{1-4} hydrocarbyloxy and C_{1-4} hydrocarbyl optionally substituted by C_{1-2} alkoxy or hydroxy.

38. A compound according to claim 36 or claim 37 wherein R^1 is unsubstituted or is substituted by 0, 1, 2, 3 or 4 substituents, preferably 0, 1, 2 or 3, and more preferably 0, 1or 2 substituents.

39. A compound according to claim 38 wherein the group R^1 has one or two substituents selected from fluorine, chlorine, trifluoromethyl, methyl and methoxy.

40. A compound according to claim 39 wherein R^1 is a mono-chlorophenyl or dichlorophenyl group.

41. A compound according to any one of the preceding claims wherein R^4 is selected from hydrogen and methyl.

42. A compound according to any one of the preceding claims wherein R^5 is selected from hydrogen, fluorine, chlorine, bromine, methyl, ethyl, hydroxyethyl, methoxymethyl, cyano, CF_3, NH_2, $NHCOR^{9a}$ and $NHCONHR^{9a}$ where R^{9a} is phenyl or benzyl optionally substituted by hydroxy, C_{1-4} acyloxy, fluorine, chlorine, bromine, trifluoromethyl, cyano, C_{1-4} hydrocarbyloxy and C_{1-4} hydrocarbyl optionally substituted by C_{1-2} alkoxy or hydroxy.

43. A compound according to any one of the preceding claims wherein R^2 and R^3 are independently selected from hydrogen, C_{1-4} hydrocarbyl and C_{1-4} acyl.

44. A compound according to claim 43 wherein R^2 and R^3 are independently selected from hydrogen and methyl.

45. A compound according to claim 44 wherein R^2 and R^3 are both hydrogen.

46. A compound according to any one of the preceding claims having a molecular weight no greater than 1000, more usually less than 750, for example less than 700, or less than 650, or less than 600, or less than 550.

47. A compound according to claim 46 wherein the molecular weight is less than 525 and, for example, is 500 or less.

48. A compound of the formula (I) as defined in any of the examples herein.

49. A compound according to any one of the preceding claims in the form of a salt, solvate (such as a hydrate), ester or N-oxide.

50. A compound as defined in any one of claims 1 to 49 for use in the prophylaxis or treatment of a disease state or condition mediated by protein kinase B.

51. The use of a compound as defined in any one of claims 1 to 49 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by protein kinase B.

52. A method for the prophylaxis or treatment of a disease state or condition mediated by protein kinase B, which method comprises administering to a subject in need thereof a compound as defined in any one of claims 1 to 49.

53. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, which method comprises administering to the mammal a compound as defined in any one of claims 1 to 49 in an amount effective in inhibiting abnormal cell growth.

54. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, the method comprising administering to the mammal a compound as defined in any one of claims 1 to 49 in an amount effective to inhibit PKB activity.

55. A method of inhibiting a protein kinase B, which method comprises contacting the kinase with a kinase-inhibiting compound as defined in any one of claims 1 to 49.

56. A method of modulating a cellular process by inhibiting the activity of a protein kinase B using a compound as defined in any one of claims 1 to 49.

57. A method for treating an immune disorder in a mammal, the method comprising administering to the mammal a compound as defined in any one of claims 1 to 44 in an amount effective to inhibit PKB activity.

58. A compound as defined in any one of claims 1 to 49 for use in the prophylaxis or treatment of a disease state or condition mediated by protein kinase A.

59. The use of a compound as defined in any one of claims 1 to 49 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by protein kinase A.

60. The use of a compound of the formula (I) as defined in any one of claims 1 to 49 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition arising from abnormal cell growth.

61. The use of a compound of the formula (I) as defined in any one of claims 1 to 49 for the manufacture of a medicament for the prophylaxis or treatment of a disease in which there is a disorder of proliferation, apoptosis or differentiation.

62. A method for the prophylaxis or treatment of a disease state or condition mediated by protein kinase A, which method comprises administering to a

subject in need thereof a compound as defined in any one of claims 1 to 49.

63. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, the method comprising administering to the mammal a compound as defined in any one of claims 1 to 49 in an amount effective to inhibit PKA.

64. A method of inhibiting a protein kinase A, which method comprises contacting the kinase with a kinase-inhibiting compound as defined in any one of claims 1 to 49.

65. A method of modulating a cellular process by inhibiting the activity of a protein kinase A using a compound as defined in any one of claims 1 to 44.

66. A method for treating an immune disorder in a mammal, the method comprising administering to the mammal a compound as defined in any one of claims 1 to 49 in an amount effective to inhibit PKA activity.

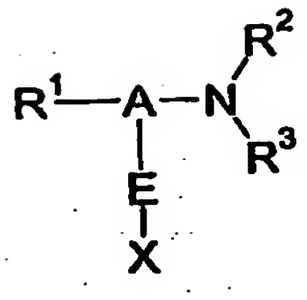
67. A method of inducing apoptosis in a cancer cell, which method comprises contacting the cancer cell with a compound as defined in any one of claims 1 to 49.

68. A pharmaceutical composition comprising a novel compound as defined in any one of claims 1 to 44 and a pharmaceutically acceptable carrier.

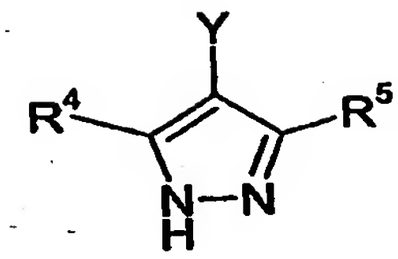
69. A compound as defined in any one of claims 1 to 49 for use in medicine.

70. A process for the preparation of a compound of the formula (I) as defined in any one of claims 1 to 48, which process comprises:

(a) the reaction of a compound of the formula (X) with a compound of the formula (XI) or an N-protected derivative thereof:



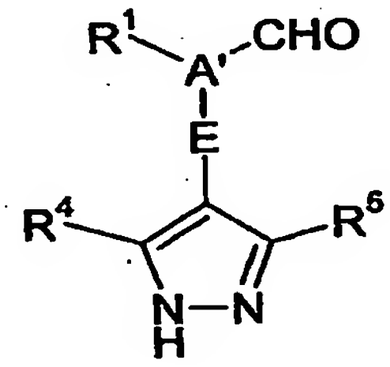
(X)



(XI)

wherein A, E, and R^1 to R^5 are as defined in any one of the preceding claims, one of the groups X and Y is selected from chlorine, bromine, iodine and trifluoromethanesulphonate, and the other one of the groups X and Y is a boronate residue, for example a boronate ester or boronic acid residue, in the presence of a palladium catalyst and a base;

(b) the reductive amination of a compound of the formula (XXXVI):



(XXXVI)

with HNR^2R^3 in the presence of a reducing agent.